AR201-13466

COURTNEY M. PRICE
VICE PRESIDENT
CHEMSTAR

American Chemistry Council *Good Chemistry Makes It Possible*

December 20, 2001

Ms. Christine Todd Whitman, Administrator
U.S. Environmental Protection Agency
PO Box 1473
Merrifield, VA 22116

Subject: HPV Chemical Challenge Program – Test Plan Submission for Consortium #

Dear Adminstrator Whitman:

The American Chemistry Council's Aliphatic Esters Panel (Panel) submits for review and public comment its test plan, as well as related robust summaries, for the "Aliphatic Esters" category of chemicals under the Environmental Protection Agency's High Production Volume (HPV) Chemical Challenge Program. The Panel understands that there will be a 120-day review period for the test plan and that all comments generated by or provided to EPA will be forwarded to the Panel for consideration.

The Aliphatic Esters category consists of 45 chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. Within this category, there are 5 groups of chemicals. These groups are based on similarities such as: common functional groups; the likelihood of common precursors and/or breakdown products, via physical or biological processes, which result in structurally similar chemicals; and incremental and constant changes across the groups. The Panel believes that this category meets the Challenge Program's definition of a chemical category.

The Panel has given careful consideration to the animal welfare principles contained in the EPA's October 14, 1999, letter to HPV Challenge Program participants. As directed, the Panel has sought to maximize the use of existing data for scientifically appropriate related chemicals and structure-activity-relationships. Additionally, the Panel has conducted a thoughtful, qualitative analysis rather than use a rote checklist approach in analyzing the adequacy of existing data.

The Panel intends to fulfill all the Screening Information Data Set (SIDS) endpoints of the HPV program through the use of existing data. In addition, some endpoints have been

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completed through the utilization of data from studies conducted on structurally similar compounds and from modeling programs accepted by the EPA. The Panel believes these data are adequate to satisfy the requirements of the HPV program without the need for new or additional tests.

John Morris of my staff is the technical contact for this Panel. Should you have any questions or comments, please contact him at 703-741-5631 (Phone), 703-741-6091 (Fax) or John_Morris@americanchemistry.com (e-mail).

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

Attachment

cc: O. Hernandez, EPA
C. Auer, EPA
Aliphatic Esters Panel
Steven Russell, ACC
Jim Keith, ACC

AR201-13466A

HIGH PRODUCTION VOLUME (HPV)

CHEMICAL CHALLENGE PROGRAM

TEST PLAN

FOR

ALIPHATIC ESTERS CATEGORY

Prepared by:

American Chemistry Council's
Aliphatic Esters Panel

December 17, 2001

three HPV monoesters and the six reference alkyl fatty acid esters, it was justifiable to utilize the available data to "read-across" and to bridge the toxicity data gaps for the HPV esters in Group A. No additional mammalian and environmental toxicity testing are proposed for this group.

Group B - Aliphatic esters, comprised of diacids and monoalcohols - "Diesters"

Thirteen HPV aliphatic esters fell into Group B. The distinguishing feature of this group is that they are diester derivatives of the common diacids: namely, maleic (C4), adipic (C6), azelaic (C9) and sebacic (C10) acids. The alcohol portion in most of the diesters falls in the C7-C13 carbon number range. In addition, a majority of the HPV diesters in this group fall within the carbon range of C22-C32 and have similar properties and structural characteristics. The diesters in this group have widespread use as lubricants, plasticizers, and solvents.

In addition to the available data for various HPV diesters in this group, there was published information for other structurally related diesters which provided useful supplementary data to help bridge the toxicity data gaps for the other HPV diesters. The non-HPV reference compounds included: maleic acid, dibutyl ester; adipic acid, di-C7-9 branched and linear alkyl ester; adipic acid, bis(2-ethylhexyl) ester; and adipic acid, dibutyl ester.

Measured physicochemical property data were available for many of the diesters. In addition, computer estimation models were used to calculate physicochemical property and environmental fate data for the Group B substances. The calculated data were obtained using the EPIWIN and EQC models that the EPA has cited for use in the HPV Chemical Challenge Program. The experimental and calculated values were sufficient to provide the necessary information on the physicochemical and fate properties of the HPV esters in Group B. No additional testing for physicochemical and fate properties is proposed for this group.

The available datasets of mammalian toxicity information (e.g., acute, repeated dose, genetic toxicity, reproductive/developmental toxicity) from both the HPV diesters and the non-HPV reference compounds were sufficient to cover the SIDS data endpoints for the range of diesters in this group and to permit "read-across" assessment for untested HPV members. Especially useful were the extensive toxicity data available for maleic acid, dibutyl ester; adipic acid, bis(2-ethylhexyl) ester; adipic acid, tridecyl ester; and adipic acid, di-C7-9 branched and linear alkyl esters; sebacic acid, bis(2-ethylhexyl) ester. These diesters covered the carbon number range for the HPV diesters in this group and provided useful toxicity data to make "read-across" assessments and to bridge data gaps. No additional mammalian toxicity testing is proposed for this group.

Similarly, sufficient aquatic toxicity and biodegradation data were available from both the HPV diesters and the non-HPV reference diesters to cover the carbon-number range within this group and to allow for "read-across" assessments of aquatic toxicity and biodegradation for the other HPV members. No additional environmental toxicity and biodegradation testing are proposed for this group.

Group C - Aliphatic esters, comprised of monoacids and dihydroxy alcohols - "Glycol Esters"

Eight HPV aliphatic esters were organized into Group C. The differentiating feature of this group is that they are ester derivatives of ethylene glycol and propylene glycol (the alcohol portion of the ester molecule). Fatty acids (C6-C18) make up the carboxylic acid portion of the ester molecule,

with oleic and stearic acids being the most common. The HPV glycol esters covered the C20-C40 carbon number range. The commonalities of the ethylene glycol or propylene glycol substructure and the natural fatty acids (e.g., oleic and stearic acids) justify grouping the HPV glycol esters together on toxicological grounds. The glycol esters have widespread use in lubricant, cosmetic and solvent applications.

The published data on five structurally related non-HPV glycol esters were also reviewed and were used as supplementary information to help bridge the toxicity of substances in this group. These non-HPV reference glycol esters included: heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol; triethylene glycol, diheptanoate; propylene glycol, monostearate; propylene glycol, dilaurate; and propylene glycol, diisostearate. It should be noted that the propylene glycol stearates, oleates and laurates, which are commonly used in many cosmetics, were very structurally similar to many of the HPV substances in Group C. It is noteworthy that propylene glycol stearate has been approved for a variety of pharmaceutical applications and is "Generally Recognized as Safe" (GRAS) for food use. Thus, the reference glycol ester compounds provided useful toxicity information for "read-across" assessments.

Physicochemical properties and environmental fate for all group members were calculated using appropriate QSAR models and supplemented with measured data from the literature or from company data. No additional physicochemical and fate properties studies are proposed for this group.

The available mammalian toxicity information from both the HPV glycol esters and the non-HPV reference compounds were sufficient to cover the SIDS data endpoints for the HPV substances in this group and to permit "read-across" assessments for the untested members. Taken into consideration also were the published health safety assessments for thirteen propylene glycol fatty acid esters (Johnson, 1999). To complete the reproductive/developmental health hazard assessment of this group, a technical discussion document is proposed. No additional mammalian toxicity testing is proposed for this group.

There were sufficient ecotoxicity data available to indicate that the glycol esters have a low order of acute toxicity to aquatic organisms. Available information from various studies also indicate that glycol esters in this group undergo extensive biodegradation. In addition, there were published data to indicate that the constituent free ethylene or propylene glycol and free fatty acids, generated from ester cleavage of the parent glycol esters, are likely to be extensively biodegraded. No additional environmental toxicity and biodegradability testing are proposed for substances in this group.

Group D - Aliphatic esters, comprised of monoacids and sorbitan - "Sorbitan Esters"

Six HPV aliphatic esters were organized into Group D. These substances have the distinguishing feature that sorbitan comprises the alcohol portion of the ester. Sorbitan is derived from the carbohydrate sugar, sorbitol, and has four hydroxy groups available for esterification. The acid portion of the HPV sorbitan esters is comprised mainly of natural fatty acids (e.g., lauric, stearic and oleic acids). Four of the HPV substances are sorbitan monoesters and two have multiple ester linkages (i.e., sorbitan sesquioleate and sorbitan trioleate). Three of the HPV substances (i.e., the oleate esters of sorbitan) were essentially the same except for the degree of esterification.

Sorbitan esters are non-ionic surfactant-active agents that typically find use as emulsifiers, stabilizers and thickeners in foods, cosmetics, medical products, lubricants and other applications. Many of the HPV sorbitan esters have widespread use in cosmetic and pharmaceutical applications. More importantly, a substantial amount of toxicity data and health safety information have been published for the sorbitan esters. The available mammalian toxicity data on the HPV and non-HPV sorbitan esters from the literature and from proprietary sources were sufficient to cover the SIDS data endpoints for the HPV substances in this group and to permit "read-across" assessments for the untested HPV members. Also taken into consideration were the comprehensive health safety assessment reviews reported for the sorbitan esters (Elder, 1985a; CIR, 1999). Results with sorbitan monostearate in chronic two-year feeding studies indicated that this material caused no adverse effects on gestation and fertility. Results from two reproductive/developmental studies indicated that sorbitol did not cause reproductive or developmental toxicity. To complete the reproductive and developmental health hazard assessment for the sorbitan esters of this group, a technical discussion document is proposed. No additional mammalian toxicity testing is proposed for this group.

Physicochemical properties and environmental fate for all members were calculated using appropriate QSAR models and supplemented with measured data. No additional physicochemical and fate studies are proposed for this group.

There were sufficient ecotoxicity and biodegradation data to indicate that the sorbitan esters in this group are not acutely toxic to aquatic organisms and that they are extensively biodegraded in the aerobic aqueous environment. No additional environmental toxicity and biodegradability testing are proposed for substances in this group.

Group E - Aliphatic esters, comprised of monoacids and trihydroxy or polyhydroxy alcohols (polyols) - "Polyol Esters"

Fifteen HPV aliphatic esters were classified in Group E. The substances in this group represented structurally related "polyol esters" in which the fatty acids were linked to one or more of the multiple hydroxyl groups present in the polyol (alcohol portion of ester). The polyol consisted of either pentaerythritol (PE), trimethylolpropane (TMP) or dipentaerythritol (diPE). The fatty acids ranged from C5-C18 in carbon number and often were comprised of natural fatty acids such as oleic and stearic acids. The polyol esters are used as synthetic lubricants, hydraulic fluids, and cosmetic ingredients, and often find use in high temperature applications (e.g., transformer coolants, oven chain oils, high temperature greases).

Physicochemical properties and environmental fate for all group members were calculated using appropriate QSAR models and supplemented with measured data. The experimental and calculated values were sufficient to provide the necessary information on the physicochemical and fate properties of the HPV esters in this group. No additional testing for physicochemical and fate properties is proposed.

In addition to the available data for various HPV polyol esters, there were substantial proprietary data for seven structurally related polyol esters which provided useful supplementary data to help bridge the toxicity gaps for the other HPV polyol esters. The non-HPV reference compounds included three TMP esters, three PE esters and one diPE ester. The available mammalian toxicity information (e.g., acute, repeated dose, genetic toxicity, reproductive/developmental toxicity) from

both the HPV polyol esters and non-HPV reference compounds were sufficient to cover the SIDS data endpoints for the range of polyol esters in this group and to permit "read-across" assessments for the other HPV members. The HPV ester, decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,2-propanediol, has been evaluated for reproductive/developmental toxicity. According to the sponsor of the study, the test material showed no reproductive/developmental effects. To complete the reproductive/developmental health hazard assessment of this group, a technical discussion document is proposed. No additional mammalian toxicity testing is proposed for this group.

Sufficient aquatic toxicity and biodegradation data were available from both the HPV polyol esters and the non-HPV reference polyol esters to cover the range of ester types (e.g., TMP, PE) within this group and to allow for "read-across" assessments of aquatic toxicity and biodegradation for the other HPV members. The polyol esters were not acutely toxic to aquatic organisms and they were extensively biodegraded in the aqueous environment. No additional environmental toxicity and biodegradability studies are proposed for this group.

LIST OF MEMBER COMPANIES ON THE ALIPHATIC ESTERS PANEL

The American Chemistry Council's Aliphatic Esters Panel includes the following member companies:

Aristech Chemical Corporation
Arizona Chemical Company
BASF Corporation
BF Goodrich Company
Cognis Corporation
Crompton Corporation
Cytec Industries Inc.
E.I. duPont de Nemours & Company, Inc.
ExxonMobil Chemical Company
Goldschmidt Chemical Corporation
Hercules Inc.
Inolex Chemical Company
Kaufman Holdings Corporation (formerly Hatco)
Quaker Chemical Company
Rohm and Haas Company
Stepan Company
The CP Hall Company
Uniquema
Velsicol Chemical Corporation

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- Mammalian Toxicity for the Aliphatic Esters

TEST PLAN FOR THE ALIPHATIC ESTERS CATEGORY

1.0 INTRODUCTION

The American Chemistry Council's (ACC) Aliphatic Esters Panel (Panel) and its member companies have committed voluntarily to develop a Screening Information Data Set (SIDS) (i.e., physicochemical data, environmental fate and effects, and mammalian health effects) for the "aliphatic esters" category of chemicals, listed under the Environmental Protection Agency's (EPA's) High Production Volume (HPV) Chemical Challenge Program.

This test plan sets forth how the Aliphatic Esters Panel intends to address the testing information for the 45 aliphatic ester substances listed in Table 1. The chemical structures of the aliphatic esters are given in Figure 1. The test plan identifies the individual aliphatic esters based on CAS numbers and their acid and alcohol functional structures, identifies structurally related esters that fall systematically under five group subcategories, identifies existing data of adequate quality for substances included in the group subcategories and provides our rationale for applying the available SIDS data to characterize the hazards of the category members. The objective of this effort is to identify and to adequately characterize the physicochemical properties, human health and environmental fate and effects for the aliphatic esters in compliance with the EPA HPV Chemical Challenge Program.

The document also provides the basis for the determination of chemical category and the justification for dividing the aliphatic esters in five group subcategories, based on the structurally similar carboxylic acid and alcohol functionalities.

The data from this HPV category will be used to inform the public about the potential health effects of the aliphatic esters. Developing a data matrix with reliable studies and applying justifiable read-across assessments will help provide a sufficiently robust data set to characterize the endpoints in the HPV Chemical Challenge Program without significant need for further testing. This approach to the resourceful use of existing data will help minimize the use of animals for testing and at the same time adequately assess the potential hazards in the aliphatic esters category.

2.0 DESCRIPTION FOR THE ALIPHATIC ESTERS CATEGORY

2.1 Aliphatic Esters Category Analysis

This test plan addresses 45 substances which fall under the "aliphatic esters" category within the HPV Challenge Program. These aliphatic esters have been systematically organized in five groups (Group A, B, C, D, E), based on chemical structural similarities of the carboxylic acid and alcohol groups. The Panel and its member companies believe that organization of the aliphatic esters into the five group subcategories is important and represents a rational structural approach to evaluating the existing data and to developing a stepwise strategy test plan based on consideration of chemistry and structural commonalities among each group of esters. The aliphatic ester members are presented in Table 1 by their groups, TSCA HPV designated names and CAS registry numbers. The chemical structures are depicted in Figure 1.

Table 1 **Aliphatic Esters Category Substances** ***(divided into five Groups)***

Group A: Aliphatic esters, comprised of monoacids and monoalcohols - "Monoesters"

Chemical Name	CAS Number
Palmitic acid, 2-ethylhexyl ester	29806-73-3
Stearic acid, tridecyl ester	31556-45-3
Fatty acids, tall oil, 2-ethylhexyl esters	68334-13-4

Group B: Aliphatic esters, comprised of diacids and monoalcohols - "Diesters"

Chemical Name	CAS Number
Azelaic acid, bis(2-ethylhexyl)ester	103-24-2
Maleic acid, bis(1,3-dimethylbutyl)ester	105-52-2
Sebacic acid, dimethyl ester	106-79-6
Adipic acid, bis(1-methylheptyl)ester	108-63-4
Sebacic acid, bis(2-ethylhexyl)ester	122-62-3
Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester	141-17-3
Maleic acid, bis(2-ethylhexyl)ester	142-16-5
Adipic acid, diisooctyl ester	1330-86-5
Adipic acid, diisopropyl ester	6938-94-9
Adipic acid, ditridecyl ester	16958-92-2
Adipic acid, diisodecyl ester	27178-16-1
Azelaic acid, diisodecyl ester	28472-97-1
Adipic acid, diisononyl ester	33703-08-1

Group C: Aliphatic esters, comprised of monoacids and dihydroxy alcohols -"Glycol esters"

Chemical Name	CAS Number
Oleic acid, propylene ester	105-62-4
Stearic acid, 2-hydroxyethyl ester	111-60-4
Stearic acid, ethylene ester	627-83-8
Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol	18268-70-7
9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester	42222-50-4
9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol	67989-24-6
Decanoic acid, mixed diesters with octanoic acid and triethylene glycol	68583-52-8
Heptanoic acid, oxybis(2,1-ethanediyloxy-2,1-ethanediyl) ester	70729-68-9

Group D: Aliphatic esters, comprised of monoacids and sorbitan -"Sorbitan esters"

Chemical Name	CAS Number
Sorbitan, monolaurate	1338-39-2
Sorbitan, monostearate	1338-41-6
Sorbitan, monooleate	1338-43-8
Sorbitan, sesquioleate	8007-43-0
Sorbitan, trioleate	26266-58-0
Fatty acids, coco, monoesters with sorbitan	68154-36-9

Table 1 **Aliphatic Esters Category Substances *(divided into five Groups)* (Continued)**

Group E: Aliphatic esters, comprised of monoacids and trihydroxy or polyhydroxy alcohols (polyols) – "Polyol Esters"

Chemical Name	CAS Number
Nonanoic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol	126-57-8
Decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate	11138-60-6
9-Octadecenoic acid (Z)-, 2-ethyl-2-[[(1-oxo-9-octadecenyl)oxy]methyl]-1,3-propanediyl ester, (Z)-	57675-44-2
9-Octadecenoic acid (Z)-, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol	70024-57-6
Pentaerythritrol, tetrastearate	115-83-3
Nonanoic acid, neopentanetetrayl ester	14450-05-6
Carboxylic acids, C5-9, hexaesters with dipentaerythritol	67762-52-1
Carboxylic acids, C5-9, tetraesters with pentaerythritol	67762-53-2
Fatty acids, C14-18 and C16-18 unsatd, triesters with trimethylolpropane	68002-79-9
Decanoic acid, mixed esters with heptanoic acid, isovaleric acid, octanoic acid and pentaerythritol	68130-51-8
Decanoic acid, mixed esters with heptanoic acid, octanoic acid and trimethylolpropane	68130-53-0
Fatty acids, tall oil, tetra esters with pentaerythritol	68334-18-9
Fatty acids, C5-10, esters with pentaerythritol	68424-31-7
Fatty acids, C5-10, mixed esters with pentaerythritol and valeric acid	68424-34-0
Linseed oil, ester with pentaerythritol	68648-28-2
Fatty acids, C5-10, esters with dipentaerythritol	70983-72-1

2.2 Rationalization for Organizing the Aliphatic Esters Category into Five Groups

Aliphatic esters are generally defined as reaction products of carboxylic acids and alcohols. They can be synthesized by a variety of methods. They are commercially produced for a broad range of applications (e.g., as lubricants, solvents, plasticizers, emulsifiers, cosmetic ingredients). In examining the forty five aliphatic esters on the HPV list, there were sufficient structural similarities and/or differences among the substances to warrant systematically organizing them into five group subcategories.

The justification for dividing the esters into the five groups was based on similarities in their chemical structures, which depended mainly on whether the carboxylic acid portion of the ester was derived from monocarboxylic acids, fatty acids or dicarboxylic acids (e.g., adipic,

sebacic, azeleic, maleic acid) and on whether the alcohol portion was derived from monohydroxy alcohols (monoalcohols, mainly aliphatic), dihydroxy alcohols (e.g., glycols, diols), trihydroxyl or polyhydroxy alcohols (e.g., trimethylolpropane, pentaerythritol, dipentaerythritol or sorbitan). The monoacids and diacids are aliphatic or alkenyl in nature and most of the monocarboxylic acids include common natural fatty acids such as palmitic, stearic, oleic, and linoleic acids.

In addition, the organization of the HPV aliphatic esters into five group subcategories is quite appropriate because it also helps to differentiate the esters in regards to their physicochemical properties, chemical characteristics and biological activity based on structure. For example, monoesters comprised of a simple monocarboxylic acid and a simple alcohol have a single ester linkage. For a homologous series, monoesters having alcohol portions of low carbon number (e.g., methyl, ethyl, propyl) generally are expected to have low viscosity characteristics, greater water solubility and greater volatility than monoesters having longer carbon-length (e.g., C10-C18) alcohol groups. However, as the carbon numbers in the carboxylic acid or alcohol increase, the corresponding esters are likely to have lower water solubility, greater lipophilicity, less volatility, higher boiling points, and greater thermal stability. For many aliphatic esters, their poor water solubility may be an important factor to consider in assessing aquatic toxicity.

The greater degree of esterification in polyol esters helps to explain why they have lower volatility, higher thermal stability and lower water solubility than the corresponding simple monoesters. The multiple ester linkages in the diesters, glycol esters and sorbitan esters also account for similar physicochemical properties advantages that they have over monoesters. Hence, the organization and differentiation of the esters based on group type, acid and alcohol similarities, carbon length of acid/alcohol, degree of esterification, total carbon atoms, molecular weight, homologs, etc. provide a rational structural approach to assess the existing physicochemical property and environmental fate datasets and to justify "read-across" for similar ester group types.

The differentiation of the aliphatic esters based on group subcategories is very useful in assessing the potential difference in metabolism or hydrolysis, processes which lead to the generation of relatively non-toxic metabolites or degradation products. For example, the metabolism of sorbitan monooleate yields oleic acid (natural fatty acid), and sorbitan (a carbohydrate), both of which are safe to the environment and to humans. The occurrence of natural fatty acids in many of the aliphatic esters on the HPV list should be noted, especially since these fatty acids are expected to be generated from metabolism of the parent ester in the environment or in the body. Therefore, how readily aliphatic esters are metabolized to their fatty acid and alcohol components will be important to consider when assessing their environmental and human health effects and potential toxicity. Aliphatic esters with multiple ester linkages, such as the trimethylolpropane (TMP) or pentaerythritol (PE) esters, in some cases, may be slowly metabolized, as a result of possible steric hindrance.

Enzymatic hydrolysis potential is also a key determinant in evaluating biodegradability and aquatic toxicity since many of the natural fatty acids and many of the alcohols (such as sorbitan, ethylene glycol, normal alcohols) formed from cleavage of the ester are further metabolized to CO_2 or biomass and hence are considered safe.

The Panel and its member companies believe that organization of the aliphatic esters into the five group subcategories is important and represents a rational structural approach to evaulating the existing data and to developing a stepwise strategy test plan based on consideration of chemistry and structure commonality in the ester molecule.

The discussion that follows describes the basis for the group classification and describes in more detail the structural features and chemical characteristics which uniquely distinguish the five groups of aliphatic esters.

2.3 Group Classification of Aliphatic Esters Based on Acid and Alcohol Chemical Structures

Category Analysis and Group Subcategorization

Group A - Aliphatic Esters, Comprised of Monoacids and Monoalcohols - "Monoesters"

The Group A substances are comprised of a monocarboxylic acid or fatty acid, such as palmitic, stearic, oleic and linoleic acid and a monoalcohol, such as 2-ethylhexyl alcohol or tridecyl alcohol. They are often termed as "monoesters" and are synthesized from simple aliphatic acid (e.g., fatty acids) and simple monoalcohols. Three esters on the HPV list that fall into Group A are:

Group A "Monoesters" - Chemical Name *	CAS Number	Carbon Number in acid	Carbon Number in alcohol	Total carbons in Ester	MW
palmitic acid, 2-ethylhexyl ester	29806-73-3	C16	C8	C24	369
fatty acid, tall oil, 2-ethylhexyl ester (major fatty acids in tall oil are oleic and linoleic acids)	68334-13-4	C18	C8	C26	393-395
stearic acid, tridecyl ester	31556-45-3	C18	C13	C31	467

*The esters in the above table are presented in ascending order of the total carbon numbers in the ester product rather than in the order of their CAS number as in Table 1. It is hoped that presentation of the esters based on carbon number as well as structural similarities in acid and alcohol portions of the esters will be useful for structure activity relationships for the HPV assessment of the aliphatic esters.

Group A esters differ from the other four groups because they are simple monoesters derived from a monofunctional alcohol, such as 2-ethylhexyl alcohol (C8-alcohol) or tridecyl alcohol (C13 alcohol) and fatty acids such as palmitic, stearic, oleic or linoleic acid. Metabolism of the parent esters is expected to yield the corresponding fatty acids and alcohols. The fatty acids are naturally occurring and have a low order of toxicity (Cragg 2001a,b; Chow 1999; Johnson, 1999). The biological effects for 2-ethylhexyl alcohol (BIBRA, 1990; Bevan 2001b) and tridecyl alcohol (Bevan 2001b; HPV Challenge Program 2001) have been reviewed and both have been reported to have a low order of toxicity.

Group B - Aliphatic Esters, Comprised of Diacids and Monoalcohols – "Diesters"

The Group B substances are comprised of aliphatic esters derived from linear diacids and monofunctional alcohols. The diacids include maleic (C4), adipic (C6), azelaic (C9) and sebacic (C10) acid. The monofunctional alcohols most common in the diesters are in the C8 to C13 carbon range, although methyl, isopropyl and butyl occur in some diesters. Thirteen esters on the HPV list that fall into Group B are:

Group B "Diesters" - Chemical Name *	CAS Number	Carbon Number in diacid	Carbon Number in alcohol	Total carbons in diester	MW
Maleic acid, bis(1,3-dimethylbutyl)ester	105-52-2	C4	C6	C16	284
Maleic acid, bis(2-ethylhexyl)ester	142-16-5	C4	C8	C20	341
Adipic acid, diisopropyl ester	6938-94-9	C6	C3	C12	230
Adipic acid, diisooctyl ester	1330-86-5	C6	C8	C22	370
Adipic acid, bis(1-methylheptyl)ester	108-63-4	C6	C8	C22	370
Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester	141-17-3	C6	C8	C22	435
Adipic acid, diisononyl ester	33703-08-1	C6	C9	C24	399
Adipic acid, diisodecyl ester	27178-16-1	C6	C10	C26	427
Adipic acid, ditridecyl ester	16958-92-2	C6	C13	C32	511
Azelaic acid, bis(2-ethylhexyl)ester	103-24-2	C9	C8	C25	412
Azelaic acid, diisodecyl ester	28472-97-1	C9	C10	C29	469
Sebacic acid, dimethyl ester	106-79-6	C10	C1	C12	230
Sebacic acid, bis(2-ethylhexyl)ester	122-62-3	C10	C8	C26	469

*The esters in the above table are presented in ascending order of the total carbon numbers and by diester type (e.g., maleate, alipate, azelate, and sebacate) rather than in the order of their CAS number as in Table 1. It is hoped that presentation of the esters based on carbon number as well as structural similarities in acid and alcohol portions of a homologous series for the diesters will be useful for structure activity relationships for the HPV assessment of the aliphatic esters.

There are two maleic acid, seven adipic acid, two azelaic acid and two sebacic acid diesters on the HPV list. Due to the physicochemical properties of the diesters (e.g., viscosity, pour point), they have widespread applications as lubricants, solvents, and plasticizers. The linear diacid portion of the diester contributes to the good viscosity index while branching in the alcohol portion provides good pour point characteristics. Because diesters have good polarity characteristics, they are useful as solvents. Most of the diesters in Group B are higher alkyl (>C8) adipates, azelates and sebacates and these diesters generally have a low order of toxicity (David et al., 2001).

Metabolism of the diesters in animals is expected to lead to the generation of corresponding diacids: namely, maleic, adipic, azelaic and sebacic acid and the corresponding linear or branched alcohol (e.g., 2-ethylhexyl, 1-methylheptyl, isooctyl, isononyl, isodecyl, tridecyl alcohols). These diacids and alcohols can further be metabolized and conjugated to products that are excreted in the urine (Cragg 2001a,b; Bevan 2001b; Thurman 1992). The diacids and alcohols have a low order of toxicity (Cragg, 2001a,b; Bevan 2001 a,b; HPV, 2001).

Group C - Aliphatic Esters, Comprised of Monoacids and Dihydroxy alcohols - "Glycol Esters"

The Group C substances are comprised of a monocarboxylic acid (generally natural fatty acids, e.g., oleic, stearic, C6-C10 fatty acids) and a dihydroxy alcohol (glycol or diol such as ethylene glycol, polyethylene glycol, propylene glycol, 2,2-dimethyl-1,3-propanediol). These esters are often referred to as "glycol or diol esters" or as "alkylidene or alkanediyl esters". Eight esters on the HPV list that fall into Group C are:

Group C "Glycol Esters" - Chemical Name *	CAS Number	Carbon Number in Acid	Carbon Number in dihydroxy alcohol	Total carbons in Ester	MW
Stearic acid, 2-hydroxyethyl ester	111-60-4	C18	C2	C20	329
Heptanoic acid, oxybis(2,1-ethanediyloxy-2,1-ethanediyl) ester	70729-68-9	C7	C8	C22	419
9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol	67989-24-6	C18	C5	C23	368
Decanoic acid, mixed diesters with octanoic acid and triethylene glycol	68583-52-8	C8, C10	C6	C24	431
Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol	18268-70-7	C8	C8	C24	447
Stearic acid, ethylene ester	627-83-8	C18	C2	C38	595
Oleic acid, propylene ester	105-62-4	C18	C3	C39	605
9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester	42222-50-4	C18	C5	C41	633

*The esters in the above table are presented in ascending order of the total carbon numbers in the ester product rather than in the order of their CAS number as in Table 1. It is hoped that presentation of the esters based on carbon number as well as structural similarities in acid and alcohol portions of the esters will be useful for structure activity relationships for the HPV assessment of the aliphatic esters.

The rationale for grouping the glycol or diol esters is that they represent the ethylene/propylene glycol diesters in which the hydroxyl groups in the glycol are functionalized as ester derivatives. Esterification of the glycol with fatty acids such as stearic and oleic acid provides glycol diesters in the 38 to 41 carbon number range (MW 595-633), which typically make them relatively non-volatile and high boiling liquids with limited water solubility and with sufficient polar characteristics to make them useful as lubricants and solvents. In the case of the tri- and tetraethylene glycol diesters, the ether linkage in the polyalkylene portion of the glycol also imparts additional polar character to these glycol esters (Reck, 1999).

Glycol esters are susceptible to hydrolysis, both chemically and enzymatically (e.g., esterases in blood and serum, lipases and esterases in the gastrointestinal tract), yielding the corresponding free glycol (e.g., ethylene glycol, propylene glycol, or 2,2-dimethyl-1,3-propanediol) and fatty acids. The toxicity of these glycols has been extensively reviewed, especially for ethylene glycol (Cavender 2001). Propylene glycol has a low order of toxicity and has been used in humans as a diluent or solvent for water-insoluble drugs (Hardman-Goodman&Gilman, 2001).

Group D - Aliphatic Esters, Comprised of Monoacids and Sorbitan - "Sorbitan Esters"

The Group D substances are esters of monoacids, mainly common fatty acids, and sorbitan (which is derived from sorbitol - a natural carbohydrate sweetener). The fatty acids include lauric, stearic, oleic acids and coco fatty acids (mainly lauric and myristic acids). The hydroxy group in the sorbitan represents the alcohol portion of the ester linkage. Six esters on the HPV list that fall into Group D are:

Group D " Sorbitan Esters" - Chemical Name *	CAS Number	Carbon Number in Acid	Carbon Number in Alcohol	Total carbons in Ester	MW
Sorbitan, monolaurate	1338-39-2	C12	C6	C18	346
Fatty acids, coco, monoesters with sorbitan (main fatty acids are lauric and myristic acids)	68154-36-9	C12 C14	C6 C6	C18 to C20	346-374
Sorbitan, monostearate	1338-41-6	C18	C6	C24	431
Sorbitan, monooleate	1338-43-8	C18	C6	C24	430
Sorbitan, sesquioleate	8007-43-0	C18	C6	C33	569
Sorbitan, trioleate	26266-58-0	C18	C6	C60	958

*The esters in the above table are presented in ascending order of the total carbon numbers in the ester product rather than in the order of their CAS number as in Table 1. It is hoped that presentation of the esters based on carbon number as well as structural similarities in acid and alcohol portions of the esters will be useful for structure activity relationships for the HPV assessment of the aliphatic esters.

The Group D esters are carbohydrate-derived esters since the ester linkage is connected to the hydroxy group(s) of sorbitan. Of the six aliphatic esters in Group D, four have single ester linkages (i.e., sorbitan monoester). There can be multiple ester linkages, as in the case of sorbitan sesquioleate and sorbitan trioleate. Multiple ester linkages with long-chain fatty acids increase lipophilicity and also tend to diminish water solubility. The sorbitan esters are non-ionic surfactant-active agents that typically find use as emulsifiers, stabilizers, and thickeners in foods, cosmetics and medical products.

Sorbitan esters do not represent a toxicological concern since they are derived from naturally occurring materials and the parent esters are ultimately metabolized back to these same natural constituents: namely, sorbitan and common fatty acids, both of which have low orders of toxicity (Elder, 1985a; CIR, 1999).

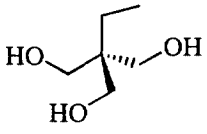
Group E - Aliphatic Esters, Comprised of Monoacid and Trihydroxy or Polyhydroxy Alcohols – "Polyol Esters"

The Group E substances are esters of monoacids, mainly common fatty acids, and trihydroxy or polyhydroxy alcohols or polyols, such as pentaerythritol (PE), 2-ethyl-2-(hydroxymethyl)-1,3-propanediol or trimethylolpropane (TMP), and dipentaerythritol (diPE). The Group E substances often are referred to as "polyol esters." The polyol esters are unique in their chemical characteristics since they lack β-tertiary hydrogen atoms, thus leading to stability against oxidation and elimination. The fatty acids often range from C5-C10 to as high as C18 (e.g., oleic, stearic, isostearic, tall oil fatty acids) in carbon number and generally are derived from naturally occurring sources. Group E esters may have multiple ester linkages and may include mixed esters derived from different carbon-length fatty acid mixtures. Fifteen esters on the HPV list that fall into Group E are:

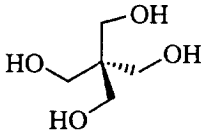
Group E "Polyol Esters" - Chemical Name *	CAS Number	Carbon Number in Acid	Total Carbons in Ester	MW
Decanoic acid, mixed esters with heptanoic acid, octanoic acid and trimethylolpropane (TMP Ester, C7, 8, 10 Acid)	68130-53-0	C7,8,10	31	513
Decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate (TMP Ester, C8, C10 Acid)	11138-60-6	C8,C10	24	415
Nonanoic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP TriEster, C9 Acid)	126-57-8	C9	33	555
Fatty acids, C14-18 and C16-18 unsatd, triesters with trimethylolpropane (TMP TriEster, C14-18 satd, C16-18 unsatd Acid)	68002-79-9	C14-18	56	875
9-Octadecenoic acid (Z)-, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP Monoester, Oleic C18 Acid)	70024-57-6	C18	24	417
9-Octadecenoic acid (Z)-, 2-ethyl-2-[[(1-oxo-9-octadecenyl)oxy]methyl]-1,3-propanediyl ester, (Z)- TMP Diester, Oleic C18 Acid)	57675-44-2	C18	60	928
Carboxylic acids, C5-9, tetraesters Pentaerythritol (PE TetraEster, C5-9 Acids)	67762-53-2	C5-9	33	523
Decanoic acid, mixed esters with heptanoic acid, isovaleric acid, octanoic acid and pentaerythritol (PE Mixed Ester, C7, 8 Acids)	68130-51-8	C7-C10	37	641
Fatty acids, C5-10, esters with pentaerythritol (PE Ester, C5-10 Acids)	68424-31-7	C5-10		613
Fatty acids, C5-10, mixed esters with pentaerhthritol and valeric acid	68424-34-0			
Nonanoic acid, neopentanetetrayl ester (PE TetraEster, C9 Acid)	14450-05-6	C9	41	697
Pentaerythritrol, tetrastearate (PE Tetraester, C18 Acid)	115-83-3	C18	77	1202
Linseed oil, ester with pentaerythritol (PE Ester, oleic, linoleic, linolenic acids)	68648-28-2	C18	77	1188
Fatty acids, tall oil, tetra esters with pentaerythritol (PE TetraEster, C18 oleic and linoleic acids)	68334-18-9	C18	77	1190
Fatty acids, C5-10, esters with dipentaerythritol (DiPE Ester, C5-10 Acids)	70983-72-1	C5-10	60	927
Carboxylic acids, C5-9, hexaesters with dipentaerythritol (diPE Esters, C5-C9 Acids)	67762-52-1	C5-9	60	955

*The esters in the above table are presented according to type of polyol ester (e.g., TMP, PE or diPE ester) and carbon number range of fatty acids in the ester rather than in the order of their CAS number as in Table 1. It is hoped that presentation of the esters based type of polyol ester and on fatty acid carbon numbers as well as structural similarities in acid and alcohol portions of the esters will be useful for structure activity relationships for the HPV assessment of the aliphatic esters.

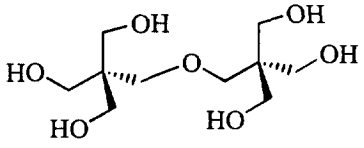
The lack of β-tertiary hydrogen atoms in the structure of the polyol esters makes them characteristically and chemically stable against oxidation and elimination in comparison to other ester classes or groups. For these reasons, trimethylolpropane (TMP) and pentaerythritol (PE) esters with fatty acids of C5 to C10 carbon-chain length have applications as synthetic lubricants for passenger car motor oil and military and civilian jet engines. TMP and PE esters of C18 acids (e.g., isostearic and oleic acids) also have found use in synthetic lubricant applications, including refrigeration lubricants and hydraulic fluids. Because of their higher thermal stability characteristics, they also find use in a variety of high temperature applications such as industrial oven chain oils, high temperature greases, fire resistant transformer coolants and turbine engines (Randles, 1999; Eisenhard, 1999).



Trimethylolpropane (TMP) or
2-ethyl-2(hydroxymethyl)-1,3-propanediol.



Pentaerythritol (PE)



Dipentaerythritol (diPE)

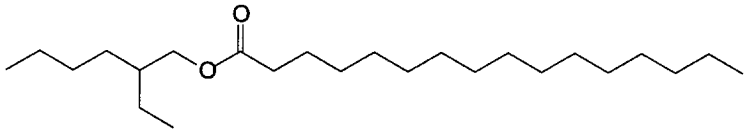
Polyol esters that are extensively esterified also have greater polarity, less volatility and enhanced lubricity characteristics. Depending on the degree of esterification, the polyol esters can be resistant or slow towards chemical or enzymatic hydrolysis (i.e., esterase or lipases) as a result of steric hindrance. PE and diPE esters that are capable of being enzymatically hydrolyzed will generate pentaerythritol or dipentaerythritol, and the corresponding fatty acids which, for most of the Group E esters, are comprised mainly of oleic, linoleic and stearic acids as well as the fatty acids in the C5-10 carbon-length. Similarly, TMP esters can undergo metabolism to yield trimethylolpropane (2-ethyl-2-hydroxymethyl-1,3-propanediol) and fatty acid constituents. Pentaerythritol and trimethylolpropane have been reported to have a low order of toxicity (Proctor and Hughes, 1996; RTECS 2001; BIBRA, 1987).

Figure 1 Chemical Structures of Aliphatic Esters

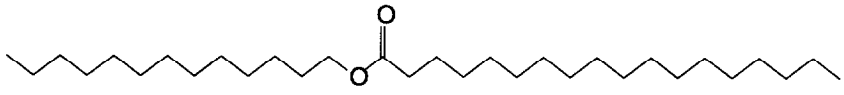
(Note: In some HPV aliphatic esters, there may be possible isomers or the material may be a mixture of components. In general, the chemical structure(s) depicted for each HPV substance represent what is believed to be the predominant isomer or component.

Group A: Aliphatic esters, comprised of monoacids and monoalcohols - " Monoesters"

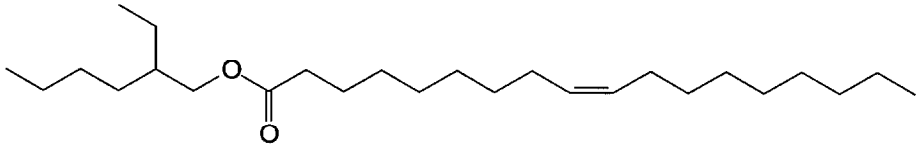
Palmitic acid, 2-ethylhexyl ester (CAS 29806-73-3)

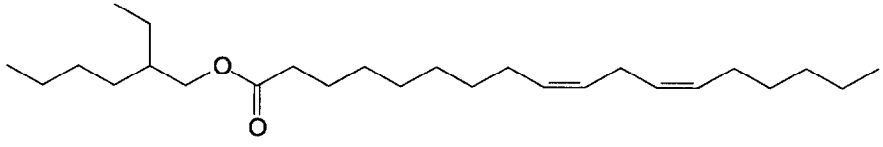


Stearic acid, tridecyl ester (CAS 31556-45-3)



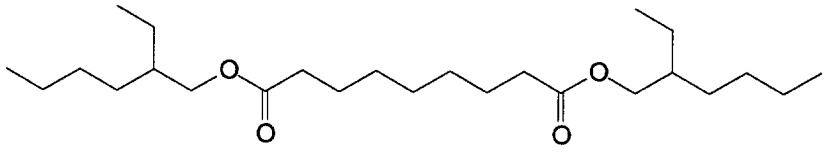
Fatty acids, tall oil, 2-ethylhexyl esters (CAS 68334-13-4)



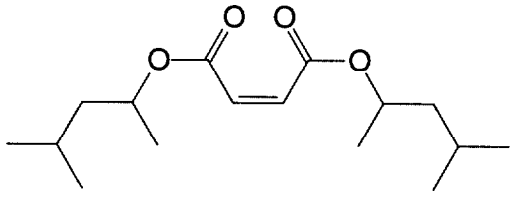


Group B: Aliphatic esters, comprised of diacids and monoalcohols - "Diesters"

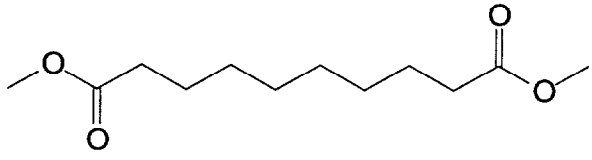
Azelaic acid, bis(2-ethylhexyl)ester (CAS103-24-2)



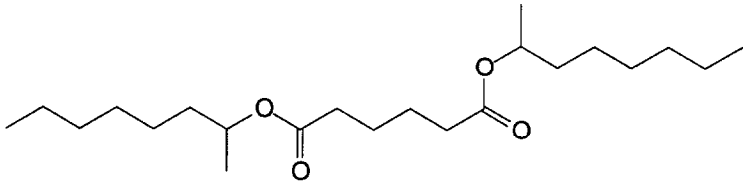
Maleic acid, bis(1,3-dimethylbutyl)ester (CAS 105-52-2)



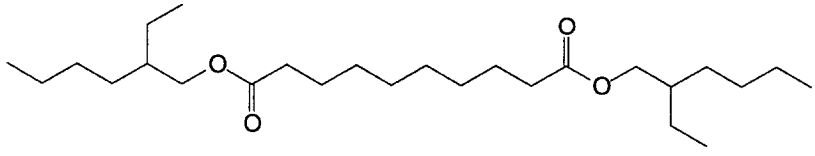
Sebacic acid, dimethyl ester (CAS 106-79-6)



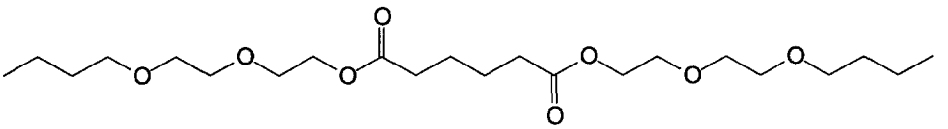
Adipic acid, bis(1-methylheptyl)ester (CAS 108-63-4)



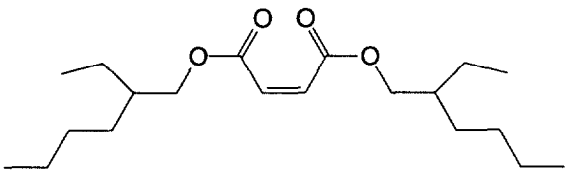
Sebacic acid, bis(2-ethylhexyl)ester (CAS 122-62-3)



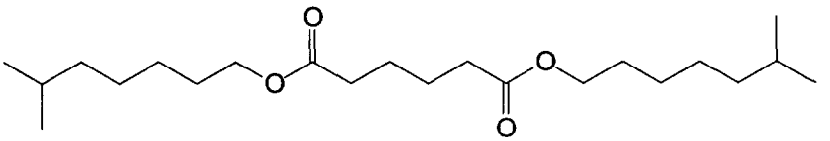
Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester (CAS 141-17-3)



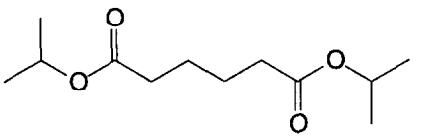
Maleic acid, bis(2-ethylhexyl)ester (CAS 142-16-5)



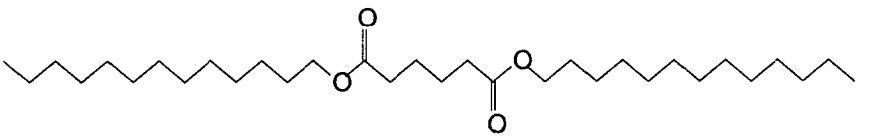
Adipic acid, diisooctyl ester (CAS 1330-86-5)



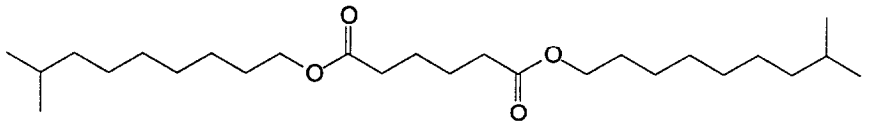
Adipic acid, diisopropyl ester (CAS 6938-94-9)



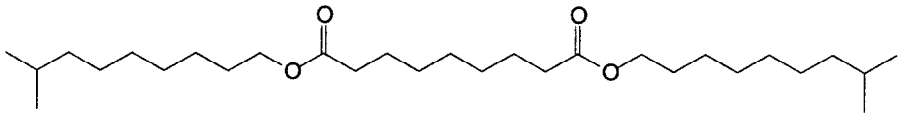
Adipic acid, ditridecyl ester (CAS 16958-92-2)



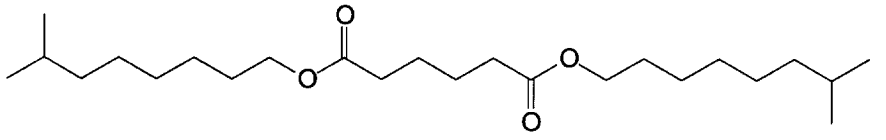
Adipic acid, diisodecyl ester (CAS 27178-16-1)



Azelaic acid, diisodecyl ester (CAS 28472-97-1)

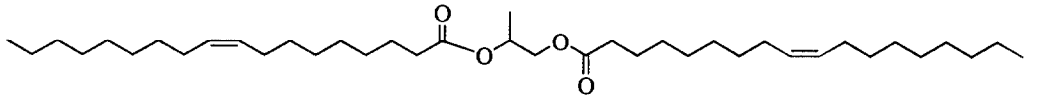


Adipic acid, diisononyl ester (CAS 33703-08-1)

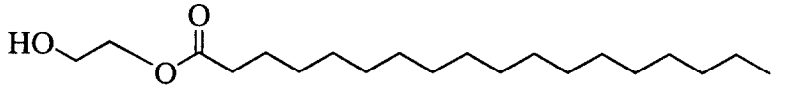


Group C: Aliphatic esters, comprised of monoacids and dihydroxy alcohols - "Glycol Esters"

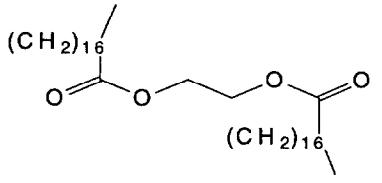
Oleic acid, propylene ester (CAS 105-62-4)



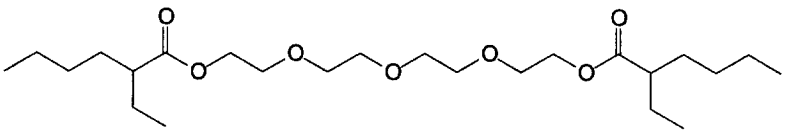
Stearic acid, 2-hydroxyethyl ester (CAS 111-60-4)



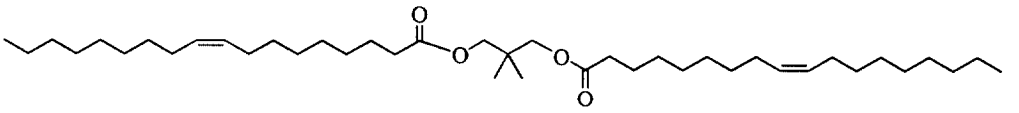
Stearic acid, ethylene ester (CAS 627-83-8)



Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol (CAS 18268-70-7)

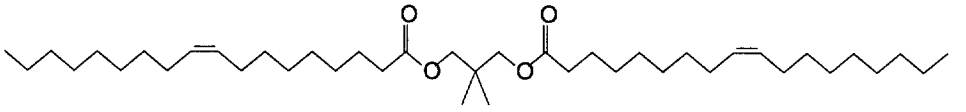


9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester (CAS 42222-50-4)

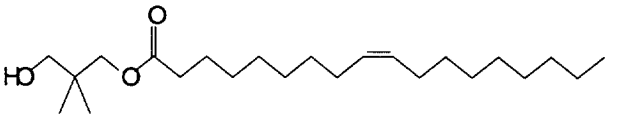


9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (CAS 67989-24-6)

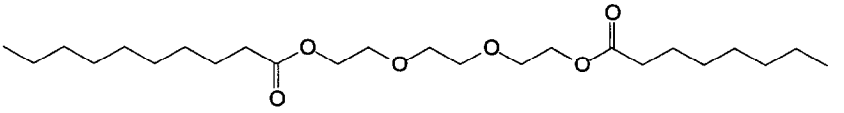
Major (88%)



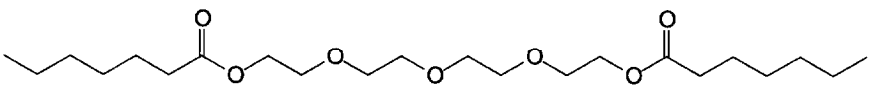
Minor (12%)



Decanoic acid, mixed diesters with octanoic acid and triethylene glycol
(CAS 68583-52-8)

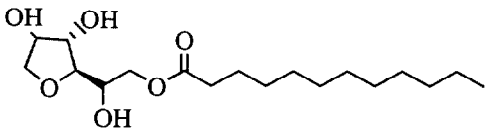


Heptanoic acid, oxybis(2,1-ethanediyloxy-2,1-ethanediyl) ester
(CAS 70729-68-9)

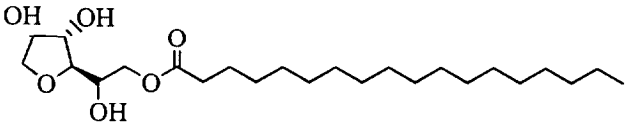


Group D: Aliphatic esters, comprised of monoacids and sorbitan - "Sorbitan Esters"

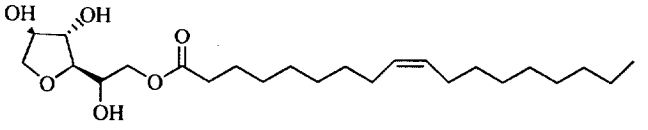
Sorbitan, monolaurate (CAS 1338-39-2)



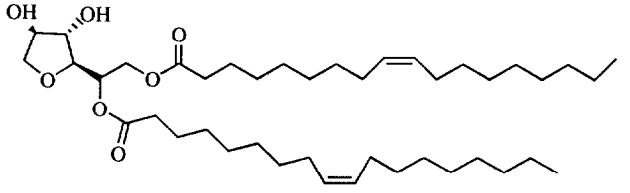
Sorbitan, monostearate (CAS 1338-41-6)

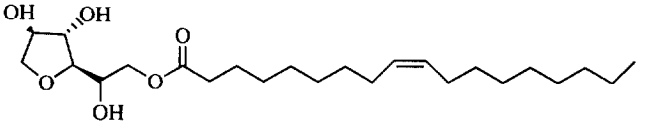


Sorbitan, monooleate (CAS 1338-43-8)

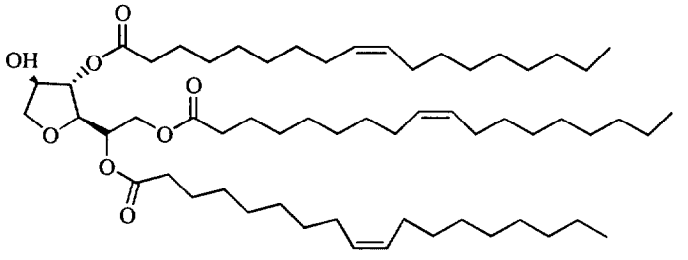


Sorbitan, sesquioleate (CAS 8007-43-0)
is mixture of monooleate and dioleate (~1:1 ratio)

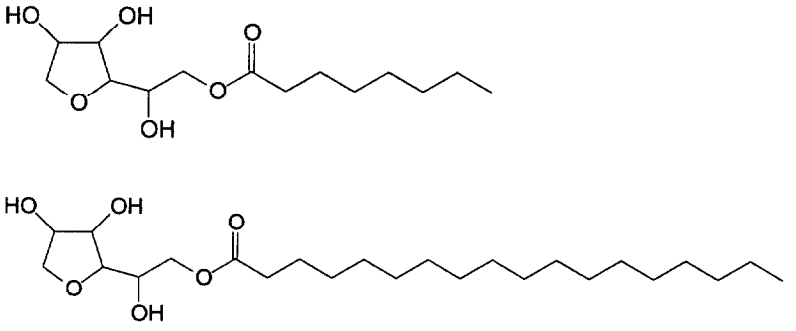




Sorbitan, trioleate (CAS 26266-58-0)

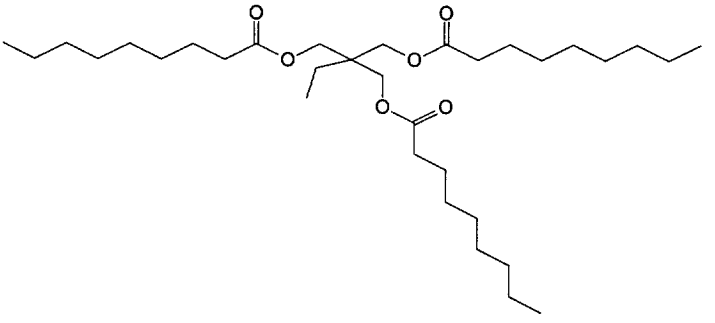


Fatty acids, coco, monoesters with sorbitan (CAS 68154-36-9)

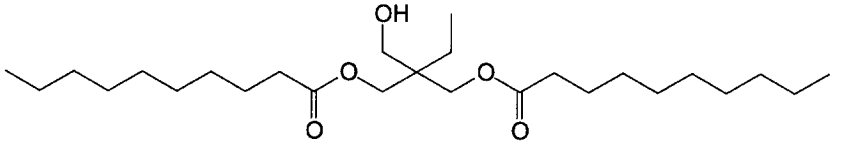


Group E: Aliphatic esters, comprised of monoacids and trihydroxy or polyhydroxy alcohols (polyols) - "Polyol Esters"

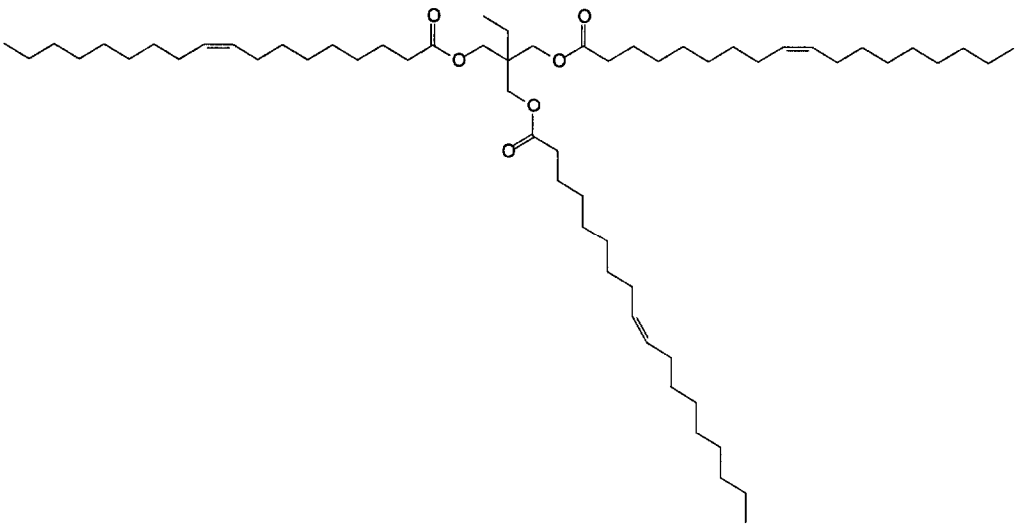
Nonanoic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (CAS 126-57-8)



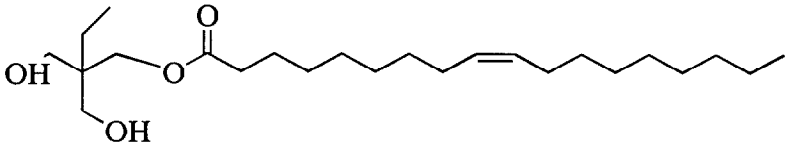
Decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate (CAS 11138-60-6)



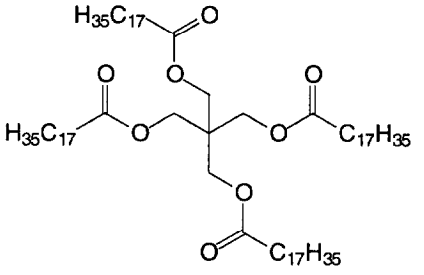
9-Octadecenoic acid (Z)-, 2-ethyl-2-[[(1-oxo-9-octadecenyl)oxy]methyl]-1,3-propanediyl ester, (Z)- (CAS 57675-44-2)



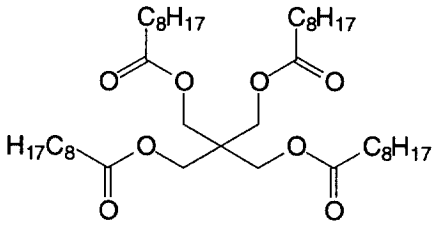
9-Octadecenoic acid (Z)-, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (CAS 70024-57-6)



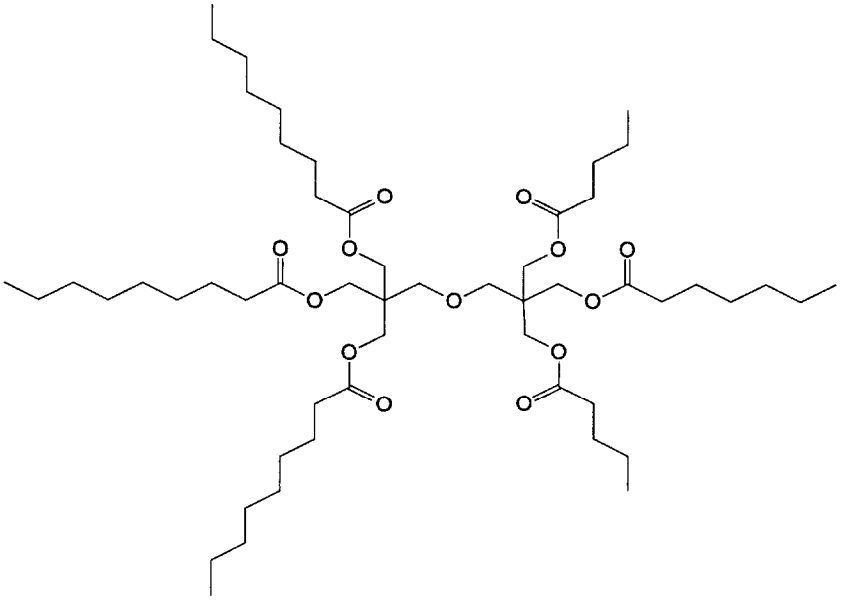
Pentaerythritol, tetrastearate (CAS 115-83-3)



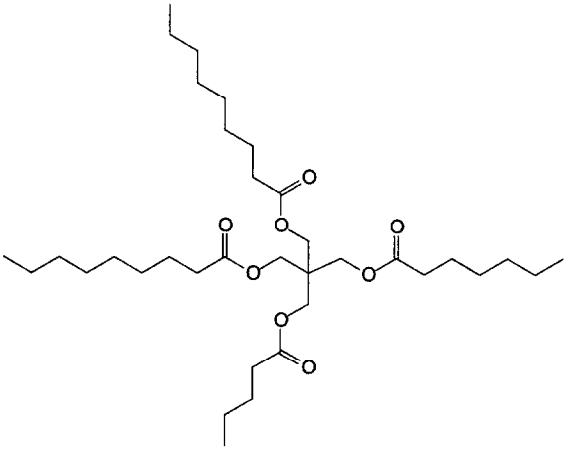
Nonanoic acid, neopentanetetrayl ester (CAS 14450-05-6)



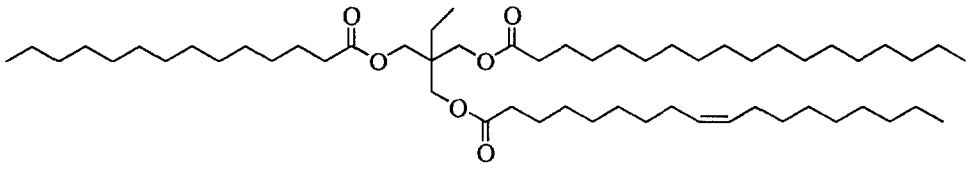
Carboxylic acids, C5-9, hexaesters with dipentaerythritol (CAS 67762-52-1)



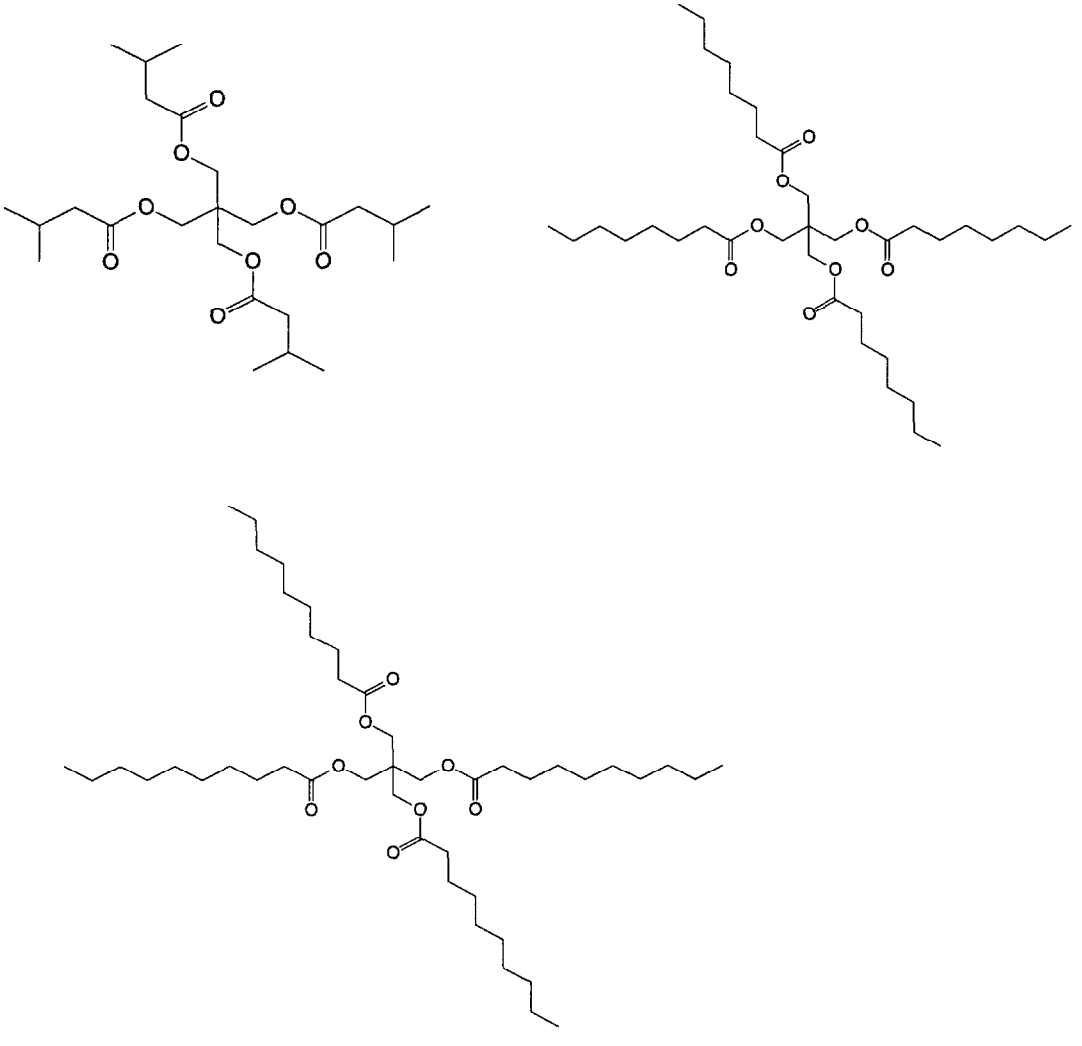
Carboxylic acids, C5-9, tetraesters with pentaerythritol (CAS 67762-53-2)



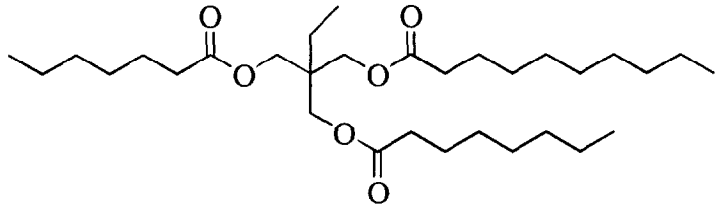
Fatty acids, C14-18 and C16-18 unsatd, triesters with trimethylolpropane (CAS 68002-79-9)



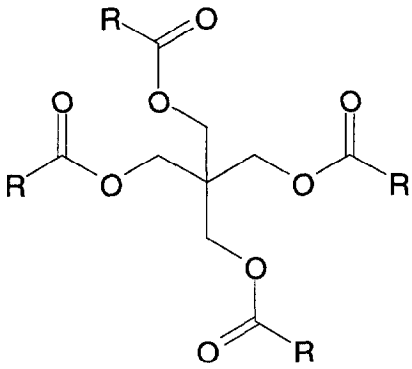
Decanoic acid, mixed esters with heptanoic acid, isovaleric acid, octanoic acid and pentaerythritol (CAS 68130-51-8)



Decanoic acid, mixed esters with heptanoic acid, octanoic acid and trimethylolpropane (CAS 68130-53-0)



Fatty acids, tall oil, tetra esters with pentaerythritol (CAS 68334-18-9)

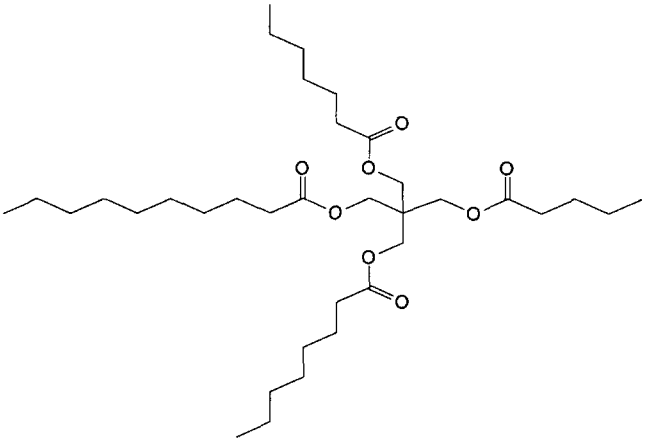


R = predominantly (70-90%) a mixture of

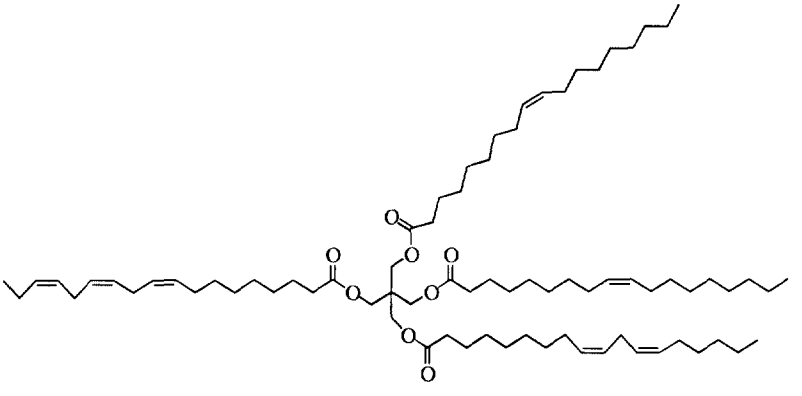
——$(CH_2)_7CH=CHCH_2CH=CH(CH_2)_4CH_3$ and

——$(CH_2)_7CH=CH(CH_2)_7CH_3$

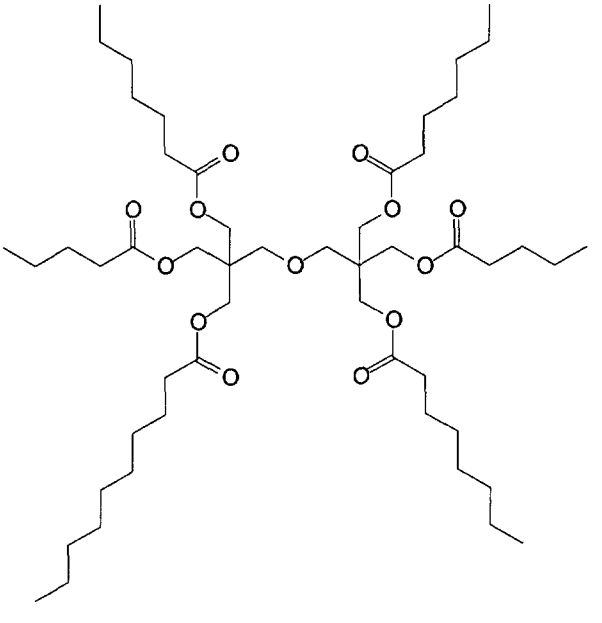
Fatty acids, C5-10, esters with pentaerythritol (CAS 68424-31-7)



Fatty acids, C5-10, mixed esters with pentaerythritol and valeric acid (CAS 68424-34-0)
--to be added in revised version
Linseed oil, ester with pentaerythritol (CAS 68648-28-2)



Fatty acids, C5-10, esters with dipentaerythritol (CAS 70983-72-1)



3.0 EVALUATION OF AVAILABLE PUBLIC AND COMPANY DATA

A review of the literature and company data was conducted on the physicochemcial properties, environmental fate and effects, and mammalian toxicity endpoints for the 45 aliphatic ester chemicals, using CAS numbers and chemical names. Searches included the following sources: MEDLINE and TOXLINE databases; the TSCATS database for relevant unpublished studies on these chemicals; and standard handbooks and databases (e.g., Sax, CRC Handbook on Chemicals, IUCLID, Merck Index, etc.) for physicochemical properties.

The reports were selected for review based on the following criteria: relevant SIDS endpoint, relevant CAS number, final report of company study (TSCATS), peer reviewed journal, or comprehensive reviews (e.g. Patty's Toxicology, 2001). Several comprehensive safety assessment reviews were found in the literature (i.e., Cosmestic Ingredient Review; J. Amer. College Toxicol.; J. Internat. Toxicol.) for the sorbitan esters, propylene glycol fatty acid esters, adipates and monoesters (e.g., alkyl stearates and oleates). Esters that were chemically or structurally related (e.g., homologs, similar carbon numbers or molecular weight) to the HPV aliphatic esters were reviewed as to whether they were relevant for read-across for environmental fate, aquatic toxicity or mammalian toxicity.

Physicochemical Properties:

Modeled data were entered into the robust summaries for all of the physical properties. There are a number of reasons for this approach:

- The EPA guidance (www.epa.gov/opptintr/chmrtk/robsumgd.htm) allows inclusion of calculated values in the robust summaries for physicochemical elements.
- There was a need for a complete set of physical property data in order to calculate environmental distribution.
- There were data gaps for physical properties for a few of the aliphatic esters.

The physical properties were modeled using the SRI/EPA computer program EPIWIN, a modeling package that includes a number of algorithms developed at or for the EPA. EPIWIN is the program used and advocated by the EPA. Because the model is a structure-property model, a specific discreet structure is required. EPIWIN contains a CAS number database which contains the structures for a large number of chemicals. For mixtures, a single representative structure is contained in the database and in this work, these surrogate chemical structures were accepted for further modeling. It should be remembered that the resultant physicochemical properties are for a single structure and not a mixture so the values are discreet numbers rather than ranges.

Environmental Toxicity:

The environmental data selected for review were primarily obtained through the literature or propietary data. Once the study was identified, a review was performed of the original study document and a robust summary was prepared.

Mammalian Toxicity:

The existing data for the mammalian toxicity endpoints were reviewed using the literature searches to identify the most relevant studies for each chemical in the group. A number of the individual chemicals on the list had no relevant studies identified in the searches. For the listed chemicals that contained relevant data, all available studies were reviewed using the criteria outlined in the EPA's methods for determining the adequacy of existing data for the HPV program and the ranking system proposed by Klimisch et al. (1997). The most relevant studies that were available for the mammalian health endpoints are presented in the Appendices.

Studies that were chosen for robust summaries represented the best available data for a particular SIDS endpoint. Published studies from the general literature, as well as a number of unpublished company reports, were obtained and summarized. Some endpoints include multiple study summaries in order to present a more complete data set. Some of the reported studies (particularly older acute data) could not be summarized because of limited or insufficient experimental detail to assess their quality or only were reported as LD_{50} values from secondary sources. These studies are included in the summary data tables.

4.0 TESTING RATIONALE

Group A - Aliphatic Esters, comprised of Monoacids and Monoalcohols - "Monoesters"

Three HPV aliphatic esters were organized together in Group A because they represent simple "monoesters", comprised of natural fatty acids and a long-chain monoalcohol (2-ethylhexyl and tridecyl alcohol). Six other long alkyl fatty acid esters not on the HPV list were also reviewed because they were structurally related and provided useful data for predicting the toxicity of substances in this group.

The non-HPV long-chain alkyl fatty acid esters were:

- Butyl stearate (CAS 123-95-5),
- Octyl stearate (CAS 109-36-4),
- Decyl oleate (CAS 3687-46-5),
- Myristyl stearate (CAS 17661-50-6),
- Isocetyl stearate (CAS 25339-09-7) and
- Fatty acid, C16-18 saturated and C18 unsaturated, 2-ethylhexyl ester (CAS 85049-37-2).

Physicochemical Properties

The physicochemical properties for the three esters were calculated using EPIWIN and are summarized in Table 2A. Since the three HPV substances are higher fatty acid esters, they would be expected to be rather lipophilic (log Pow 10-14) in character due to the large number of carbon numbers in the ester molecule (e.g., 24, 26, 31 carbons) and they would be expected to have relatively high boiling points. Owing to the non-volatile nature of these esters, their vapor pressures would be expected to be very low and difficult to determine experimentally. Water solubility of the three HPV monoesters was calculated to be very low.

The six non-HPV long-chain alkyl fatty acid esters were also examined and their experimental and calculated (EPIWIN) data also included for comparison. Comparison of the six non-HPV esters indicates that as a general category, most of the alkyl fatty acid esters have high MW (369 to 494), high b.p. (>350°C), high log P (9.7 to 15.5), and very low water solubility.

In addition, hydrolysis half lives and atmospheric photodegradation rates were calculated by EPIWIN. The monoester hydrolysis rates were determined to be quite low and not a significant environmental fate route. Environmental distribution was determined using the EQC (Equilibrium Criterion) model (Mackay, et al. 1996). Fugacity modeling indicates that the fatty acid esters have similar distribution patterns in the environmental compartments (e.g., air, water, soil, sediment) .

On the basis of these results, no additional measurements of the physicochemical or fate properties of the Group A esters are necessary.

Mammalian Toxicity

Acute Toxicity. Available acute toxicity data indicate that the fatty acid esters in Group A, in general, have a low order of toxicity [e.g., palmitic acid, 2-ethylhexyl ester (LD50 > 5 g/kg) and tall oil fatty acid 2-ethylhexyl ester (LD50 > 64 g/kg)]. Consistent with that, available data spanning the carbon range of C22 to C34 indicate that the alkyl fatty acid esters are not

toxic by oral administration [rat LD50 (oral) > 5g/kg, with range from 5 g/kg to 64 kg/kg]. Butyl stearate is tolerated by rats without lethal effects at oral doses of 32 g/kg while octyl oleate has a reported LD50 of >40 ml/kg. In addition, many alkyl fatty acid esters, such as the stearates, oleates and palmitates, have been demonstrated to be not toxic by dermal administration (Elders et al. 1982, 1985). Many higher fatty acid esters, such as the stearates, oleates and palmitates, have been cleared for use in the food industry (Bisesi, 2001); thus, their general physiological response and toxicity are very low. Many of the higher fatty acid esters are considered safe for use in cosmetics (Elders, 1985). Because of the low volatility of these substances, inhalation exposure at toxicological significant levels is not expected. Hence, further testing of substances in this group for acute toxicity is not proposed.

Repeated Dose Toxicity. 28-Day oral gavage studies in rats with decyl oleate (CAS 3687-46-5) at doses of 100, 500 and 1000 mg/kg showed no toxicity as noted with respect to clinical symptoms, biochemistry, hematology, gross lesions or tissue/organ histopathology (IUCLID, 1996). The NOAEL was estimated to be 1000 mg/kg. Similarly, octyl or (2-ethylhexyl) stearate showed a NOAEL of 1000 mg/kg in 28-day oral gavage studies in rats. In chronic two-year feeding studies with butyl stearate at concentrations of 1.25% or 6.25% in the diet, exposed rats showed no significant difference from control animals with respect to growth, survival, blood counts or other hematological parameters. Besides the two substances above, various other long-chain fatty acid esters have also been studied for their repeated dose toxicity and the findings support a low order of toxicity (see reviews by Elder, 1982a,b; 1985; Bisesi, 2001). For this reason, further testing of substances in this group for repeated dose toxicity is not necessary.

Genetic Toxicity (Salmonella). Although the HPV esters have not been tested, three of the non-HPV ester surrogates [fatty acid, C16-18 saturated and C18 unsaturated, 2-ethylhexyl ester (CAS 85049-37-2); octyl stearate (CAS 109-36-4); and decyl oleate (CAS 3687-46-5)] were shown to be negative in the Ames assay. Since the monoesters are similar in chemical structure and carbon-number range, it is unlikely that esters in Group A will induce point mutation. In addition, the chemistry of the long-chain fatty acids does not suggest the likelihood that these substances or their constituent substructures (i.e., fatty acids, alcohols) are reactive or electrophilic in nature. Hence, further testing for point mutation is not necessary.

Genetic Toxicity (Chromosomal Aberrations). No information has been reported. As discussed above for point mutation, the chemistry of the long-chain fatty acid esters does not suggest the likelihood that these substances or their constituent substructures (i.e., fatty acids, alcohols) are reactive or electrophilic in nature. Therefore, the likelihood that the fatty acid monoesters may cause chromosomal mutation is very low. A technical discussion document is proposed to address the issue that fatty acid monoesters are not expected to be electrophilic based on their inherent chemistry and therefore, not likely to cause chromosomal aberrations. Thus, no further genetic toxicity testing for chromosomal aberration is proposed for this group.

Toxicity to Reproduction. Assessment of reproductive effects of alkyl fatty acid esters in Group A is based primarily on studies with butyl stearate. Elders (1985) reported that fertility, litter size and survival of offspring were normal in rats fed diets containing 6.25% butyl stearate for 10 weeks. However, growth was reduced in offspring during the pre-weaning and post-weaning periods. No gross lesions were noted among the offspring killed at the end of the 21-day post-weaning periods These results indicate that long-chain fatty acid esters do not cause reproductive toxicity in rats. Given the relative low order of toxicity for long-chain

fatty acid esters and their relative non-electrophilic and non-reactive nature, it seems unlikely that the long-chain fatty acid esters would present serious reproductive concerns. Therefore, no further reproductive toxicity testing is proposed for substances in this group.

Developmental Toxicity/Teratogenicity. Assessment of developmental effects for the long-chain fatty acid esters in this group was based primarily on data reported for fatty acid, C16-18, 2-ethylhexyl ester (CAS 91031-48-0). In oral gavage studies in rats administered doses of 100, 300 and 1000 mg/kg during gestation, the maternal NOAEL was > 1000 mg/kg and the NOAEL for teratogenicity was >1000 mg/kg. Based on these findings and the fact that the two HPV substances, palmitic acid, 2-ethylhexyl ester (CAS 29806-73-3) and fatty acid, tall oil, 2-ethylhexyl ester (CAS 68334-13-4), are very chemically similar to the structure of the tested material, fatty acid, C16-18, 2-ethylhexyl ester (CAS 91031-48-0), read-across assessment is appropriate. For this reason, no further testing for developmental toxicity is warranted.

Environmental Toxicity and Biodegradation

Although no ecotoxicity data are available for the three HPV esters, aquatic toxicity results have been reported for two structurally similar alkyl fatty acid esters [i.e., decyl oleate and fatty acid, C16-18 saturated and C18 unsaturated, 2-ethylhexyl ester]. These two non-HPV esters are not acutely toxic to fish (LL50 3200 mg/L). In daphnids, the acute LL50 was reported to be 17 mg/L and in algae, the LL50 was reported to be 40-42 mg/L based on biomass and growth rate endpoints. Because of their limited water solubility, the alkyl fatty acid esters and Group A esters are not likely to cause acute aquatic toxicity. As a consequence, no further aquatic testing is necessary.

Biodegradation of alkyl fatty acid esters are expected to occur extensively based on the reported 28 day test results (80-85% biodegradation, OECD 301D) for decyl oleate and for the 2-ethylhexyl ester of C16-18 saturated and C18 unsaturated fatty acids (CAS 85049-37-2). The HPV esters would be expected to be extensively biodegraded since the fatty acids in these esters are primarily comprised of palmitic, stearic or oleic acids, which are known to be rapidly biodegraded (Verschueren, 1996). Based on the above findings and the chemical similarity of the tested substances with the three HPV substances, no further biodegradability testing is necessary.

Overview

As described earlier, there are three HPV substances organized in Group A. The distinguishing feature of these HPV aliphatic esters is that they represent simple "monoesters", comprised of monocarboxylic acids (ranging from C14-C18, typically natural fatty acids) and simple monoalcohols (ranging from C8-C13). The three HPV aliphatic esters are in the carbon range of C24-C31 and they are very similar structurally to a number of alkyl fatty acid esters that are used extensively in the cosmetic industry [e.g., butyl stearate (CAS 123-95-5), octyl stearate (CAS 109-36-4), decyl oleate (CAS 3687-46-5), myristyl stearate (CAS 17661-50-6), and isocetyl stearate (CAS 25339-09-7)]. There is an adequate database of toxicological information available for these non-HPV long-chain alkyl fatty acid esters. Given the similar chemical/structural features between the three HPV monoesters and the non-HPV alkyl fatty acid esters, this available data would be useful for assessing the Group A substances. Therefore, it is reasonable to presume that the data from the extensively tested alkyl fatty acid esters can be used to predict the toxicological properties of the less studied HPV

Group A chemicals. The chemical structure similarities between the two justify such "read-across" assessments.

Physicochemical properties and environmental fate information are provided in Table 2A. A summary of the available toxicology data is shown in Table 3A. No additional testing is proposed for Group A.

Group A	Acute	Repeat dose	Genetic tox (mutation)	Genetic tox (chrom ab)	Reprod	Develop	Acute fish	Acute daphnia	Algal	Biodeg
Stearic acid, butyl ester *	√	√	R	TD	√	R	R	R	R	R
Palmitic Acid, 2-EH ester	√	R	R	TD	R	R	R	R	R	R
Fatty Acid, tall oil, 2-EH ester	√	R	R	TD	R	R	R	R	R	R
Fatty Acid, C16-18 satd, C18 unsatd, 2-EH esters*	√	R	√	TD	R	√	√	√	√	√
Stearic Acid, octyl ester*	√	√	√	TD	R	√	R	R	R	R
Oleic Acid, decyl ester *	√	√	√	TD	R	R	√	√	√	√
Stearic Acid, tridecyl ester	R	R	R	TD	R	R	R	R	R	R
Stearic Acid, myristyl ester*	√	R	R	TD	R	R	R	R	R	R
Stearic Acid, isocetyl ester*	√	R	R	TD	R	R	R	R	R	R

* Not U.S. HPV aliphatic ester; data included for read-across to other group category members
The clinical safety of many of the non-HPV alkyl fatty acid esters have been extensively reviewed by the Cosmetic Ingredient Review Expert Panel (see Elder 1982a,b; 1985).

Abbreviations in table: √ = adequate data; R = read-across, TD = Technical Discussion Proposed

Group B - Aliphatic Esters, comprised of Diacids and Monoalcohols - "Diesters"

Thirteen HPV alipatic esters were organized in Group B. These substances were grouped together since they are structurally related "diesters" derived from common organic diacids such as adipic, maleic, azelaic and sebacic acids. In addition, many of the diesters fell within the carbon range of C22-C32 and had similar properties and structural characteristics. Four other diesters, not on the HPV list, were also reviewed because they were structurally similar and provided useful data for bridging toxicity information and for assessing (i.e., read-across) the health effects of the aliphatic esters in this group.

The four non-HPV diesters are:

- Maleic acid, dibutyl ester (CAS 105-76-0)
- Adipic acid, dibutyl ester (CAS 105-99-7)
- Adipic acid, di-C7-9 branched and linear alkyl ester (CAS 68515-75-3)
- Adipic acid, bis(2-ethylhexyl) ester (CAS 103-23-1).

Physicochemical Properties

There is a significant amount of reported experimental data for the physicochemical properties of the esters in Group B, especially the adipates (Table 2B). Computer models were also used to estimate these properties for comparison with measured values and to help predict the environmental distribution of the HPV Group B diesters and the three non-HPV adipates. The calculated data were developed using EPIWIN, a computer model that the EPA has cited for use in the HPV Challenge Program.

In general, the short-chain alkyl (e.g., methyl, isopropyl, and butyl) diesters were generally more water soluble, less lipophilic and relatively more volatile than the corresponding long-chain alkyl (C7-C13 alcohol) diesters. However, most of the diesters on the HPV list (10 of 13) have molecular weight of greater than 350, have high boiling points (>300°C) and are expected to be relatively non-volatile, lipophilic (log P > 7) and extremely water-insoluble.

The distribution between the environmental compartments for Group B diesters is influenced by the water solubility and lipophilicity. In general, for diesters with higher water solubility characteristics (e.g., diisopropyl adipate and dibutyl adipate, dimethyl sebacate), the EQC models (Mackay et al., 1996) predicted a greater distribution of the test substance in the water compartment. For more lipophilic diesters, the EQC models predicted a greater distribution in soil and sediment. Hydrolysis half-lives and atmospheric photodegradation rates were calculated using EPIWIN and are summarized in the table.

Sufficient physicochemical data exist for the Group B diesters and no additional testing is needed.

Mammalian Toxicity

Acute Toxicity. Acute toxicity data, showing a low order of toxicity, have been reported for 11 of the 13 HPV esters in Group B. Oral rat LD50 values ranged from >2 g/kg to >64 g/kg. Acute oral toxicity data have also been reported for the non-HPV substances. Further testing of substances in this group for acute toxicity is not necessary.

Repeated Dose Toxicity. Data on repeated dose toxicity have been reported for diisononyl adipate and tridecyl adipate. In 90-day toxicity studies, rats were administered diisononyl adipate (CAS 33703-08-1) in the diet at levels equivalent to 0, 50, 150 and 500 mg/kg/day. The NOAEL was 500 mg/kg/day. Feeding studies were also carried out in beagle dogs for 13 weeks at dietary concentrations of 0, 0.3, 1 and 3% (increased to 6% at week 9). The NOAEL was determined to be 1% in the diet or approximately 274 mg/kg/day. In another 13-week study, ditridecyl adipate was well tolerated in rats given dermal doses of 800 and 2000 mg/kg/day.

In addition, 90-day subchronic dietary studies have been carried out with two non-HPV adipates: namely, adipic acid di-C7-9 branched and linear alkyl ester (CAS 68515-75-3) and adipic acid, bis(2-ethylhexyl) ester (CAS 103-23-1). For adipic acid di-C7-9 branched and linear alkyl ester (CAS 68515-75-3), rats were fed 0, 0.1, 0.5 and 2.5% of the test substance in the diet. No significant signs of toxicity were observed in male and female rats administered the test material in the diet at concentrations up to 2.5% for a period of 13 weeks. The NOAEL was 2.5% for both sexes (males ~1300 mg/kg; females ~1800 mg/kg). In the 90-day dietary studies with 2-ethylhexyl adipate (CAS 103-23-1), the NOAEL was ~300 mg/kg/day in rats and ~230 mg/kg/day in mice. The LOAEL was ~600 mg/kg/day in rats and ~460 mg/kg/day in mice. Hepatic hypertrophy and increased peroxisomal enzyme activity occurred in rats and mice; however, there were no adverse effects on the liver. Repeated oral gavage studies (7-day) have been reported also for dibutyl maleate (Table 3B).

Sufficient subchronic toxicity data exist for diesters in the C12-C32 carbon range, from the studies carried out to date. Therefore, there is no need to carry out additional repeated dose toxicity studies of substances in Group B.

Genetic Toxicity (Salmonella). Three HPV substances [i.e., adipic acid ditridecyl ester, adipic acid diisononyl ester and sebacic acid bis(2-ethylhexyl) ester] were shown to be negative in the Ames assay. In addition, diisononyl adipate was negative in the mouse lymphoma assay. Adipic acid, bis(2-ethylhexyl) ester (non-HPV) has also been evaluated for mutagenicity and was found to be negative in both the Ames and mouse lymphoma assays. Although the two maleate diesters have not been tested, it has been reported that dibutyl maleate (CAS 105-76-0) is negative in the Ames assay (Table 3B). As all of these diesters were inactive for mutagenicity, further testing of Group B diesters for point mutation is not warranted.

Genetic Toxicity (Chromosomal Aberrations). Adipic acid, ditridecyl ester (CAS 16958-92-2) was negative in the micronucleus assay. The non-HPV substance, adipic acid bis(2-ethylhexyl) ester (CAS 103-23-1), also did not cause chromosomal aberrations in the Chinese hamster ovary cell assay or the mouse micronucleus test (David et al. 2001). Since these two adipates cover the carbon number range of C22-C32 for the diesters, it is unlikely that the substances in Group B are chromosomal mutagens. In addition, dibutyl maleate (C12) has

been shown to be negative in the mouse micronucleus test in vivo. Therefore, no further testing for chromosomal aberrations is proposed for this group.

Toxicity to Reproduction. Di-2-ethylhexyl adipate (DEHA)(CAS 103-23-1) has been evaluated for reproductive effects in a one-generation study. Male and female rats were administered DEHA in their diets at same levels (0, 28, 170 or 1080 mg/kg/day). After 10 weeks on the diet, the animals were mated to produce one generation of offspring. Test diets were fed continuously throughout the study (18-19 weeks of exposure). No effects were seen on male or female fertility. However, at the highest dose, there was a reduction in body weight in the dams, and reduction in offspring body weight, total litter weight and litter size. The NOAEL and LOAEL for this study was 170 and 1080 mg/kg/day, respectively (ICI, 1988a). In 13-week dermal studies with ditridecyl adipate, there was no sperm morphological changes observed in male rats treated at levels of 2000 mg/kg. Increases in organ weight of the epididymides and uterus were observed at dermal exposure to 2000 mg/kg but not at 800 mg/kg. In a 19-week oral feeding study with sebacic acid, bis(2-ethylhexyl) ester (CAS 122-62-3), no adverse reproductive effects were reported for this material (BIBRA, 1996). Dibutyl maleate has been evaluated in an OECD reproductive/developmental toxicity screening test (oral gavage) and no adverse effects on reproduction were reported (OECD SIDS dossier for dibutyl maleate). Since these four materials cover the carbon number range of C12-C32 for the diesters and because of the chemical similarity of the alkyl diesters, the available reproductive toxicity data should be sufficient for read-across assessment of most of the other diesters in Group B. Therefore, no additional testing for reproductive toxicity is necessary for this group.

Developmental Toxicity/Teratogenicity. Developmental studies have been carried out with three non-HPV diesters. No evidence of developmental toxicity was observed at dose levels of 1000 and 4000 mg/kg/day after oral gavage of adipic acid, di-C7-9 branched and linear alkyl ester (CAS 68515-75-3). Slight maternal toxicity (reduced body weight) and embryotoxicity (reduced fetal weight) was observed at the highest dose (7000 mg/kg/day). The NOAEL for maternal and developmental toxicity was 4000 mg/kg/day. No adverse developmental effects were reported for dibutyl maleate in an OECD reproductive/developmental screening study.

The developmental toxicity has also been evaluated for adipic acid, bis(2-ethylhexyl) ester (CAS 103-23-1) by dietary exposure. Pregnant rats administered 2-ethylhexyl adipate in the diet throughout gestation showed reduced body weight at dietary equivalent doses of 1080 mg/kg/day. At 1080 mg/kg/day, implantation fetal loss was evident; however, no gross, skeletal or visceral abnormalities were observed. LOAEL was 1080 mg/kg/day and NOAEL was 170 mg/kg/day (developmental toxicity)(ICI, 1988b). The developmental toxicity data from these three studies provide sufficient data for the read-across assessment of most of the other diesters in Group B due to their chemical structural similarities. Therefore, no further developmental toxicity testing is proposed.

Environmental Toxicity and Biodegradation

Acute aquatic toxicity studies have been carried out with five of the HPV diesters and three of the non-HPV adipates. There is sufficient information on the toxicity data in fish, invertebrates and algae for many of the Group B aliphatic esters (Table 3B). The diesters included maleates, adipates, azelates and sebacates in the carbon range of C12-C32, which basically bridges most of the 13 diesters.

In general, the tested diesters did not cause acute toxicity to aquatic organisms. Since the long-chain length diesters have very limited water solubility, these materials are probably not likely to cause toxicity at their maximum water solubility. For example, no mortality was reported in fish, daphnia and algae at water saturation levels for 2-ethylhexyl adipate. Since the matrix set of available aquatic toxicity data provides sufficient information for read-across assessment of most of the other diesters in Group B, no further aquatic toxicity testing is needed.

Biodegradability results have been reported for seven of the 13 HPV diesters as well as for the non-HPV diesters. Most of the tested diesters were readily biodegradable which indicates that long-chain diesters are capable of undergoing very extensive biodegradation in aqueous aerobic environments. Although there are differences in the overall percent biodegradation among the diesters, this is not unexpected given potential structural differences (e.g., degree of branching in alcohol portion of molecule) and given water solubility limitations for many of the diesters. Regardless, the information available for the matrix set indicates that diesters are extensively biodegraded. Dimethyl maleate and dibutyl maleate have been reported to undergo rapid biodegradation (>95% in 28 days) (IUCLID, 1996; OECD SIDS dossier for dibutyl maleate). Therefore, short-chain alkyl diesters such as diisopropyl and dibutyl adipates and dimethyl sebacate would also be expected to be biodegraded to a similar extent. Since there are sufficient experimental data reported, which covered the range of diesters on the HPV list, no additional biodegradability testing is necessary.

Overview

As discussed earlier, thirteen HPV aliphatic esters were organized into Group B. The distinguishing chemical feature of this group of substances is that they are ester derivatives of the common diacids: namely, maleic (C4), adipic (C6), azelaic (C9) and sebacic (C10) acids. The alcohol portion in most of the diesters falls in the C7-C13 carbon number range and they typically have branched structural features. Ten of the 13 HPV diesters fall in the C20-C32 carbon range; for this reason, most of the diesters have high boiling points, low volatility, low water-solubility and high lipophilic characteristics. The shorter-chain alkyl diesters (e.g., dimethyl sebacate, diisopropyl and dibutyl adipates) have greater water solubility, greater volatility and lower lipophilicity than the corresponding long-chain (C7-C13) alkyl diesters.

Other non-HPV diesters, especially maleic acid, dibutyl ester; adipic acid, di-C7-9 branched and linear alkyl ester; and adipic acid, bis(2-ethylhexyl) ester, have been extensively tested. They are included in this review mainly because they provide useful toxicological data for assessing the Group B substances. Collectively, the seven HPV adipates and the three non-HPV adipates represented a broad homologous series of diesters that was useful in the matrix analysis of the HPV substances. The chemical structure similarities among the diesters justify

grouping these substances together on toxicological grounds. The physicochemical, environmental and toxicological data from the HPV and the non-HPV materials cover the majority of carbon numbers in the diesters in Group B.

Physicochemical properties and environmental fate information are provided in Table 2B. A summary of the available toxicology data is shown in Table 3B. No additional testing is proposed for Group B.

Group B	Acute	Repeat dose	Genetic tox (mutation)	Genetic tox (chrom ab)	Reprod	Develop	Acute fish	Acute daphnia	Algal	Biodeg
Maleic acid, dibutyl ester *	√	√	√	√	√	√	√	√	√	√
Maleic acid, bis(1,3-dimethylbutyl)ester	√	R	R	R	R	R	R	R	R	R
Maleic acid, bis(2-ethylhexyl)ester	√	R	R	R	R	R	R	R	R	R
Adipic acid, diisopropyl ester	√	R	R	R	R	R	R	R	R	R
Adipic acid, dibutyl ester *	√	R	R	R	R	R	R	R	R	R
Adipic acid, di-C7-9 branch and linear alkyl esters*	√	√	√	R	R	√	√	√	√	R
Adipic acid, diisooctyl ester	√	R	R	R	R	R	R	R	R	√
Adipic acid, bis(1-methylheptyl)ester	√	R	R	R	R	R	R	R	R	R
Adipic acid, bis(2-ethylhexyl)ester*	√	√	√	√	√	√	√	√	√	√
Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester	R	R	R	R	R	R	R	R	R	R
Adipic acid, diisononyl ester	√	√	√	R	R	R	√	R	R	√
Adipic acid, diisodecyl ester	√	R	R	R	R	R	R	R	R	√
Adipic acid, ditridecyl ester	√	√	√	√	√	R	√	√	R	√
Azelaic acid, bis(2-ethylhexyl)ester	√	R	R	R	R	R	√	R	R	√
Azelaic acid, diisodecyl ester	√	R	R	R	R	R	√	R	R	√
Sebacic acid, dimethyl ester	R	R	R	R	R	R	R	R	R	R
Sebacic acid, bis(2-ethylhexyl)ester	√	√	√	R	√	R	√	√	√	√

* Not U.S. HPV aliphatic ester; data included for read-across to other group category members
Abbreviations in table: √ = adequate data; R = read-across

Group C - Aliphatic Esters, comprised of Monoacids and Dihydroxy Alcohols - "Glycol Esters"

Eight HPV aliphatic esters were classified in Group C based on the presence of the diol or glycol functionality which was common to all these "glycol esters". The HPV substances were ester derivatives (e.g., C6-C18 fatty acids) of, mainly, ethylene glycols or propylene glycols. Five non-HPV glycol or diol esters were also reviewed because they were chemically similar and provided useful data for bridging the toxicity of substances in this group.

The five non-HPV glycol esters were:

- Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8)
- Triethylene glycol, diheptanoate (CAS 7434-40-4)
- Propylene glycol, monostearate (CAS 1323-39-3)
- Propylene glycol, dilaurate (CAS 22788-19-8)
- Propylene glycol, diisostearate (CAS 68958-54-3)

Physicochemical Properties

The experimental and calculated physicochemical properties for the "glycol esters" in Group C are summarized in Table 2C. EPIWIN was used to estimate these properties for comparison with measured values and to help predict the environmental distribution in the various compartments.

In general, the glycol monoesters with shorter carbon-number fatty acids (C7) were more water-soluble and less lipophilic than the corresponding glycol monoesters containing long-chain fatty acids such as stearic and oleic acids. The glycol diesters were predicted to be more lipophilic and less water-soluble than the corresponding glycol monoesters (e.g., ethylene glycol monostearate *versus* distearate; propylene glycol monooleate *versus* dioleate). In addition, the glycol diesters have higher boiling points than the corresponding monoesters.

Polyglycol esters, that contain more than one repeating ethylene glycol unit, generally showed greater water solubility than the corresponding monoglycol esters, owing to the increased polarity of multiple ether linkages; this was consistent with what would be expected. The greater degree of ether linkage was also consistent with the lower lipophilicity (log P) values predicted by EPIWIN.

Most of the glycol esters on the HPV list have molecular weights of greater than 300, have high boiling points (>400 C) and showed low water solubility and high lipophilic characteristics (log P >5). The glycol distearates and dioleates had carbon numbers above C38 and high boiling points (>550 °C).

In additon, hydrolysis half lives and atmospheric photodegradation rates were calculated using EPIWIN. Environmental distribution was determined using EQC.

No further measurements of physicochemical properties or fate are needed for this group.

Mammalian Toxicity

Acute Toxicity. The available data indicate the HPV glycol esters have a low order of acute toxicity by the oral administration. The reported oral rat LD50 values ranged from 2g/kg to 34.6 g/kg. Four of the eight HPV glycol esters in Group C have been tested. In addition, acute toxicity data have been reported for many other non-HPV glycol esters. In particular, the ethylene glycol and propylene glycol esters have been extensively studied and their health safety evaluated (Andersen, 1999; Elder, 1982c, 1983). For example, propylene glycol

monostearate (CAS 1323-39-3) has an acute oral LD50 of 25.8 g/kg in rats. Propylene glycol stearate has been approved for a variety of pharmaceutical uses and is considered Generally Recognized as Safe (GRAS) for food or food contact use (Elder, 1983). Hence, further testing of substances in this group for acute toxicity is not proposed.

Repeated Dose Toxicity. Subchronic studies have been carried out with heptanoic acid, oxybis[2,1-ethanediyloxy-2,1-ethanediyl] ester (CAS 70729-68-9). In 28-day oral gavage studies in rats, the NOAEL was determined to be 1000 mg/kg. No signs of toxicity were observed and no treatment-related changes in hematology or clinical chemistry were reported.

Two non-HPV glycol esters have also been evaluated in repeated dose toxicity studies. Propylene glycol monostearate (CAS 1323-39-3), which was administered for 13 weeks at dietary concentrations of 0, 1.5%, 3.36% and 7.52%, showed no signs of toxicity in rats. Similarly, in 6-month oral studies, no signs of toxicity, gross or histological pathology were observed in rats and dogs fed diets containing up to 10% propylene glycol stearate (Elder, 1983). For another non-HPV glycol ester, heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8), doses up to 1000 mg/kg/day were well tolerated in rats that were orally (gavage) administered the test material for 28 days. Signs of toxicity were either minor, reversible or sex/species specific. Increased liver weights observed at 1000 mg/kg dose are believed to be associated with adaptive changes associated with metabolism (e.g., enzyme induction) and not toxicity as such. Hyaline droplet formation observed in the male kidneys is believed to be a sex/species condition specific to only male rats, which has little relevance to humans.

The findings from the studies above as well as other subchronic dermal toxicity studies for other propylene glycol monoesters and diesters (Elder 1982c, 1983; Johnson, 1999) indicate that there are sufficient data on the repeated dose toxicity of the glycol esters available to provide read-across assessments. Thus, no additional testing for repeated dose toxicity for substances in this group is warranted.

Genetic Toxicity (Salmonella). One HPV substance, heptanoic acid, oxybis[2,1-ethanediyloxy-2,1-ethanediyl] ester (CAS 70729-68-9), has been shown to be negative in the Ames assay. In addition, three non-HPV glycol esters [heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol; triethylene glycol diheptanoate; and propylene glycol monostearate] have been found to be negative in the Ames test as well. These findings indicate that the glycol esters do not cause point mutations. This is consistent with the chemistry of the glycol esters, which does not suggest the likelihood that these substances, or their constituent glycols or fatty acids, are electrophilic or reactive in nature. Therefore, no additional testing for point mutation for substances in this group is warranted.

Genetic Toxicity (Chromosomal Aberrations). Heptanoic acid, oxybis[2,1-ethanediyloxy-2,1-ethanediyl] ester (CAS 70729-68-9) has been evaluated and did not cause chromosomal aberrations in the Chinese hamster ovary cell assay. In addition, the non-HPV substance, heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (CAS 71839-38-8), has also been evaluated in the *in vitro* cytogenetics test using human peripheral lymphocytes. It showed negative results for chromosomal aberrations. The available information on these two substances indicates that glycol esters are not likely to cause chromosomal aberrations. This is consistent with the chemistry of the glycol esters, which does not suggest the likelihood that these substances, or their constituent glycols or fatty acids, are electrophilic or reactive in nature. Therefore, the likelihood that the glycol esters may cause chromosomal aberration is

very low. For these reasons, no further genetic toxicity testing for chromosomal aberration is necessary.

Toxicity to Reproduction. No information has been reported. However, recent comments by the Cosmetic Ingredient Review expert panel on the reproductive hazard assessments of polyethyleneglycol ethers may have particular significance and implications in the context of assessing the reproductive and developmental toxicity of the glycol esters. This panel clearly pointed out that the polyethylene diesters are chemically different from the polyethylene glycol monoalkyl ethers (Andersen, 1999). The glycol diesters do not give rise to methoxyethanol or ethoxyethanol, metabolic products which have been implicated in the reproductive and developmental toxicity associated with the polyethylene glycol ethers. These metabolites of concern arise from metabolism of the ethylene glycol monoalkyl ethers and are not expected to be produced metabolically from polymers of ethylene glycol or their ester derivatives. This suggests that reproductive/developmental toxicity concerns would not exist for the glycol diesters/monoesters in the same manner that they do for the glycol monoalkyl ethers. These distinctive differences in the chemistry and metabolism between the glycol esters and polyethylene glycol ethers need to be highlighted and emphasized in the context of reproductive and developmental toxicity. A technical discussion document will be developed to address the reproductive/developmental toxicity issue for the glycol esters in that they are not likely to cause reproductive toxicity.

Developmental Toxicity/Teratogenicity. No information has been reported. However, as discussed for reproductive toxicity, the glycol diesters are not expected to give rise to methoxyethanol or ethoxyethanol, metabolic products which have been implicated in the reproductive and developmental toxicity associated with the polyethylene glycol ethers. This suggests that reproductive/developmental toxicity concerns would not exist for the glycol esters in the same manner that they do for the glycol monoalkyl ethers. These distinctive differences in the chemistry and metabolism between the glycol esters and polyethylene glycol ethers need to be highlighted and emphasized in the context of reproductive and developmental toxicity. A technical discussion document will be developed to address the developmental toxicity issue for the glycol esters in that they are not likely to cause reproductive/ developmental toxicity.

Additional note: Johnson (1999) carried out an excellent and comprehensive safety assessment of thirteen propylene glycol esters (fatty acid C8 to C18), which not only evaluated the health effects of the glycol esters but also highlighted the non-toxicity of propylene glycol and the individual fatty acids [e.g., stearic, oleic, lauric, myristic, and caprylic/capric (C10/C9)]. It appears from this assessment that propylene glycol and the fatty acids have low orders of reproductive/developmental toxicity.

Environmental Toxicity and Biodegradation

Acute toxicity data in fish, daphnia or algae have been reported for several glycol esters including: triethylene glycol diheptanoate (CAS 7434-40-4), heptanoic acid, oxybis[2,1-ethanediyloxy-2,1-ethanediyl] ester (CAS 70729-68-9) and the oleate ester with 2,2-dimethyl-1,3-propanediol (CAS 67989-24-6). The available ecotoxicity data indicate that these glycol esters, in general, are not toxic to aquatic organisms. While the higher molecular weight glycol esters (>C38, MW 500) have not been evaluated, they are expected to be relatively non-toxic as a result of their very poor water solubility and the fact that many of the HPV substances are simply the diester homolog of the corresponding glycol monoesters. For

example, 9-octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl (di)ester (CAS 4222-50-4) is simply the diester of 9-octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (CAS 67989-24-6). The latter (i.e., monoester) has been tested and shown to be non-toxic to daphnids (LL50 ~2000 ppm). Enzymatic cleavage of the ester linkage in the diester (CAS 4222-50-4) would yield the corresponding monoester and oleic acid, both of which are not toxic to aquatic organisms. It is of interest to note that ethylene glycol and propylene glycol are not acutely toxic to aquatic organisms (Verschueren, 1996; IUCLID 1996). In addition, fatty acids (e.g., stearic and oleic acids) that may be generated from enzymatic metabolism of the glycol esters are expected to have a low order of aquatic toxicity. Hence, there are sufficient data available to allow for read-across assessment of the glycol esters and no further aquatic testing is proposed for the Group C substances.

Biodegradation studies with two HPV and two non-HPV glycol esters have been reported. These results indicate that the glycol esters are readily biodegradable. The extent of biodegradation has been reported to range from 65% to 98% in 28 days for the four glycol esters. The tested substances covered the C15-C23 carbon range for the glycol esters. Glycol esters above C30 are mainly comprised of the glycol diesters such as the dioleates and distearates, and several of the HPV substances are simply the diester homolog of the corresponding monooleate or monostearate esters. These diesters are expected to be metabolized to the corresponding monoesters, which have been demonstrated to be readily biodegradable.

Enzymatic breakdown products of the glycol esters, such as propylene glycol, ethylene glycol and their fatty acids, have been reported to be readily biodegradable (Swisher, 1987; Vershueren, 1996; IUCLID 1996). In summary, it is expected that most of the HPV glycol esters would be rapidly and extensively biodegraded in the environment. Further biodegradation testing for substances in this group is not necessary given the sufficient amount of data available for assessing the biodegradability potential of structurally similar glycol esters.

Overview

As discussed previously, eight HPV aliphatic esters have been assigned to Group C . The distinguishing chemical feature of this group of substances is that they are ester derivatives of ethylene glycol and propylene glycol (the alcohol portion of the ester molecule). Fatty acids (C6-C18) make up the carboxylic acid portion of the ester molecule, with oleic and stearic acids being the most common. The HPV glycol esters cover the C20-C40 carbon number range and most have molecular weights of greater than 300, have high boiling points (>400°C) and showed low water solubility and high lipophilic characteristics. However, available data indicate that glycol esters undergo very extensive biodegradation and they are not acutely toxic to aquatic species.

The common occurrence of the ethylene glycol or propylene glycol substructure and natural fatty acids like oleic and stearic acid justify grouping the HPV glycol esters on toxicological grounds. Additionally, many non-HPV glycol esters, such as propylene glycol stearates, oleates and laurates, which are commonly used in many cosmetics, are remarkably similar in structure to the HPV substances in Group C. It is noteworthy that propylene glycol stearate has been approved for a variety of pharmaceutical applications and is "Generally Recognized as Safe" (GRAS) for food use (Elder, 1983). Therefore, the non-HPV glycol esters included in this review were useful in providing data to help assess the toxicity of other less studied members of this group.

Physicochemical properties and environmental fate information are provided in Table 2C. A summary of the available toxicology data is shown in Table 3C. No additional testing is proposed for Group C.

Group C	Acute	Repeat dose	Genetic tox (mutation)	Genetic tox (chrom ab)	Reprod	Develop	Acute fish	Acute daphnia	Algal	Biodeg
Heptanoic acid, ester with 2,2,4 -trimethyl-1,3-pentanediol *	√	√	√	√	TD	TD	R	R	R	√
Stearic acid, 2-hydroxyethyl ester	√	R	R	R	TD	TD	R	R	R	R
Triethylene glycol, diheptanoate *	R	R	√	R	TD	TD	√	√	√	√
Propylene glycol, monostearate *	√	√	√	R	TD	TD	R	R	R	R
Heptanoic acid, oxybis(2,1-ethanediyloxy-2,1-ethanediyl) ester	√	√	√	√	TD	TD	√	√	√	√
9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol	√	R	R	R	TD	TD	R	√	R	√
Decanoic acid, mixed diesters with octanoic acid and triethylene glycol	R	R	R	R	TD	TD	R	R	R	R
Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol	R	R	R	R	TD	TD	R	R	R	R
Propylene glycol dilaurate*	√	R	R	R	TD	TD	R	R	R	R
Stearic acid, ethylene ester	√	R	R	R	TD	TD	R	R	R	R
Oleic acid, propylene ester	R	R	R	R	TD	TD	R	R	R	R
Propylene glycol diisostearate*	√	R	R	R	TD	TD	R	R	R	R
9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester	R	R	R	R	TD	TD	R	R	R	R

* Not U.S. HPV aliphatic ester; data included for read-across to other group category members
Abbreviations in table: √ = adequate data; R = read-across, TD = Technical Discussion Proposed

Group D - Aliphatic Esters comprised of Monoacids and Sorbitan - "Sorbitan Esters"

Six HPV aliphatic esters were organized under Group D. These substances have the distinguishing feature that sorbitan consititutes the alcohol portion of the ester. Sorbitan is derived from the carbohydrate sugar, sorbitol, and has four hydroxy groups available for esterification. The acid portion of the sorbitan esters is comprised mainly of fatty acids such as lauric, stearic and oleic acids. Four of the HPV glycol esters were sorbitan monoesters and two substances had multiple ester linkages (i.e., sorbitan sesquioleate and sorbitan trioleate). One non-HPV sorbitan ester, sorbitan, fatty acid C6-10 tetraester (CAS 228573-47-5), was also reviewed because it provided useful data for bridging the toxicity of substances in this group and it represented a tetraester derivative of sorbitan.

Physicochemical Properties

The measured and calculated physicochemical properties for the HPV and non-HPV sorbitan esters are summarized in Table 2D. EPIWIN was used to compute these properties for comparison with experimental values and for use in predicting the environmental distribution of the substances in this group (EQC model). Hydrolysis half-lives and atmospheric photodegradation rates were computed using EPIWIN.

The HPV sorbitan esters covered the C18-C60 carbon number range. The fatty acids ranged from C10 (lauric) to C18 (stearic and oleic) acids in these materials. The chain-length of the fatty acid in the sorbitan monoesters influenced water solubility, boiling point and lipophilicity. The degree of esterification (monooleate *versus* trioleate) will also influence these properties. Hence, the water solubility of sorbitan monolaurate (C12 acid) (CAS 1338-39-2) is predicted to be much greater than that of sorbitan monostearate or sorbitan monooleate (C18 acids). The monooleate was predicted to have greater solubility in water than the corresponding sesquioleate or trioleate ester of sorbitan.

No further measurements in physicochemical properties are necessary for substances in this group.

Mammalian Toxicity

Acute Toxicity. Acute toxicity data reported for five of the six HPV sorbitan esters indicate that they have a low order of toxicity (Table 3D). The oral LD50 in rats ranged from >15.9 g/kg to > 39.8 g/kg. In addition, sorbitan, fatty acid C6-10 tetraester (CAS 228573-47-5), a non-HPV substance, has been tested in rats and its oral LD50 value was determined to be >2 g/kg. Numerous other sorbitan esters have been studied by acute oral and dermal administration. Results from these studies support the general conclusion that sorbitan fatty acid esters have low orders of acute toxicity (Elder, 1985a; CIR, 1999). Hence, no further testing for acute toxicity is necessary.

Repeated Dose Toxicity. A large number of subchronic oral and dermal studies and chronic oral feeding studies have been carried out for sorbitan monolaurate, sorbitan monostearate and sorbitan monooleate (CIR, 1999). It is beyond the scope of this paper to discuss all the subchronic and chronic toxicity studies for these three sorbitan monoesters. The comprehensive review papers by Elder (1985a) and Andersen (CIR, 1999) should be consulted for more information on the numerous repeated dose toxicity studies carried out to date for these as well as various other sorbitan esters. A few repeated dose oral feeding studies have been highlighted in Table 3D and are briefly described below.

For sorbitan monostearate, no adverse effects were reported in rats fed 5% concentrations of the test substance in the diet for 6 weeks. The NOAEL was estimated to be 5% or approximately 2500 mg/kg/day (Hendy et al. 1978). In 16-week oral studies with sorbitan monooleate, rats were fed 0, 2.5, 5 and 10% concentrations of the test substance in the diet (Ingram et al. 1978). The LOAEL was 2.5% dietary concentration (~1800 mg/kg/day) based on increased kidney weight findings that were considered significant in both male and female rats. In 13-week feeding studies with sorbitan monolaurate in rats, the LOAEL was 2.5% or approximately 2200 mg/kg/day (Cater et al. 1978).

In 2-year feeding studies at 5, 10 and 20% in the diet, Oser et al. (1957) have reported that rats tolerated sorbitan moonostearate with no adverse effects. However, at 20%, there was a small but significant decrease on growth rate in male rates. Hence, the NOAEL was 10% in the diet or approximately 5000 mg/kg/day in rats, based on these findings. In a 80-week dietary study in mice, no adverse effects were observed for sorbitan monostearate at 2% concentration in the diet and the NOAEL was 2% or approximately 2600 mg/kg/day (Hendy et al. 1978).

Sorbitan monooleate fed to rats at 5% concentrations in the diet for 2 years showed no adverse effects on growth, hematology, clinical chemistry, survival, organ size or histopathology (ACI, 1970). The NOAEL was 5% in the diet for sorbitan monooleate in this study.

Subchronic studies have also been carried out with sorbitan, fatty acids C6-10, tetraester (CAS 228573-47-5), a non-HPV material. Oral gavage studies for 28 days at dose levels up to 1000 mg/kg /day resulted in no systemic toxicity. Therefore, the NOAEL was 1000 mg/kg/day for this tetraester.

Hence, there is a large amount of information reported for the repeated dose toxicity of the sorbitan esters (Elder, 1985a; CIR, 1999). The available data covered the range of HPV substances in this group from sorbitan laurate to sorbitan oleate. Since the sesquioleate and trioleate of sorbitan are merely multiple ester homologs of sorbitan monooleate, they would be expected to show similar effects, given their structural similarities and potential to be metabolized to the monooleate. Thus, further repeated dose toxicity testing of substances in this group is not warranted.

Genetic Toxicity (Salmonella). Sorbitan monostearate (CAS 1338-41-6) was found to be negative in the Ames assay. In addition, the non-HPV substance, sorbitan fatty acid C6-10 tetraester (CAS 228573-47-5), did not cause any mutagenic effects in the *Salmonella in vitro* test. These substances bridge the low and high carbon range of most of the sorbitan esters and the chemistry of the sorbitan esters (i.e., sorbitan/sorbitol, natural fatty acids) does not suggest the likelihood that the sorbitan esters are electrophilic or reactive in nature. Thus, it is not likely that the substances in Group D cause mutagenic effects, and therefore, no further testing for point mutations is proposed.

Genetic Toxicity (Chromosomal Aberrations). Sorbitan monostearate did not transform primary Syrian golden hamster embryo cells. As discussed above for point mutation, the chemistry of the sorbitan esters does not suggest the likelihood that these substances, or their constituent substructures (i.e., sorbitol, fatty acids) are reactive or electrophilic in nature.

Therefore, the likelihood that the sorbitan esters may cause chromosomal mutation is very low or non-existent. Thus, no further genetic toxicity testing for chromosomal aberration is proposed for this group.

Toxicity to Reproduction. Limited reproductive toxicity data have been reported for the sorbitan esters. Oser et al. (1956) have reported that in 2-year feeding studies in rats with sorbitan monostearate, there were no effects on gestation and fertility at any dose level (0, 5, 10 and 20% in the diet) but survival of the newborn animals and maternal lactation were slightly diminished at the 20% level.

It is of interest to note that multigeneration feeding studies have been carried out by MacKensie et al. (1986) to evaluate the reproductive and developmental effects of sorbitol. Male and female rats fed up to 10% sorbitol in the diet during the 96-week study had no significant adverse clinical, behavioral, or reproductive effects, and no significant gross or microscopic changes were observed. Sorbitol was also studied indirectly as part of a mixture of hydrogenated starch hydrolysates (HSH) which contained about 7% sorbitol as part of the polyhydric alcohol mixture. The HSH mixture was investigated as part of a two-year ingestion study, a multigeneration reproduction study and a teratology study. At concentrations of 18% in drinking water (3000-7000 mg/kg/day), HSH did not produce reproductive or developmental effects (Modderman, 1993). These results indicate that sorbitol does not cause reproductive/developmental toxicity in animals. Given these findings and the low order of toxicity of natural fatty acids, it seems unlikely that sorbitan esters would present reproductive and developmental toxicity concerns. A technical discussion document is proposed to address reproductive/developmental toxicity issues based on the above considerations. Therefore, no reproductive toxicity testing is proposed.

Developmental Toxicity/Teratogenicity. No information has been reported. As discussed above, it appears unlikely that sorbitan esters pose developmental toxicity concerns and the reasoning is similar to that given for reproductive toxicity. A technical discussion document is proposed to address reproductive/developmental toxicity issues for the sorbitan esters. Therefore, no developmental toxicity testing is proposed.

Environmental Toxicity and Biodegradation

Aquatic toxicity data have been reported for the sorbitan esters. Sorbitan monolaurate and sorbitan monooleate have been tested. The non-HPV substance, sorbitan fatty acid C6-10 tetraester (CAS 228573-47-5), has also been evaluated in fish, daphnia and algae. These findings indicate that the sorbitan esters are not acutely toxic to aquatic organisms. The available data covered the range of water-soluble (e.g., monolaurate) and water-insoluble sorbitan esters (e.g., C6-C10 acid tetraester). Most of the sorbitan esters have limited water solubility and for this reason are not be likely to cause acute aquatic toxicity. In addition, metabolism of sorbitan sequioleate and sorbitan trioleate will generate sorbitan monooleate, for which aquatic toxicity data exist. Thus, there is sufficient information to "read-across" for the other sorbitan esters, based on the available data and the chemical similarities of the sorbitan esters, in general. Therefore, no further aquatic testing is necessary for Group D.

The biodegradation of sorbitan monolaurate, sorbitan monooleate and sorbitan, fatty acid C6-10 tetraester (CAS 228573-47-5), has been reported. These three sorbitan esters were biodegraded to the extent of 60-70% in 28-days, which indicate these materials undergo metabolism and degradation extensively in the aerobic environment. The sorbitan esters tested covered the range of carbon numbers (C18-C38) and included relatively water soluble (i.e., sorbitan monolaurate) as well as water-insoluble [i.e., sorbitan fatty acid C6-10 tetraester (CAS 228573-47-5)] members of the group. The high degree of biodegradation (70% in 28 days) for sorbitan tetraester (CAS 228573-47-5), in spite of its poor water solubility, indicates that enzymatic cleavage of the multiple ester linkage must be taking place in order to achieve the observed level of biodegradation. This would be consistent with the fact that fatty acids (e.g., oleic, stearic acid) arising from enzymatic ester bond cleavage of the sorbitan esters would be expected to be rapidly biodegraded (Vershueren, 1996; Swisher, 1987). In addition, enzymatic ester cleavage of sorbitan trioleate and sesquioleate would lead to sorbitan monooleate, for which biodegradation data exist. Thus, there is sufficient information to "read-across" for the other sorbitan esters, based on the available data and the similarities in chemistry and metabolism. These data are considered adequate to address the biodegradability of the HPV sorbitan ester and hence, no additional biodegradation testing is necessary. .

Overview

There are six HPV aliphatic esters in Group D. These substances have the distinguishing feature that sorbitan comprises the alcohol portion of the ester. Sorbitan is derived from the carbohydrate sugar, sorbitol, and has four hydroxy groups for possible esterification. The acid portion of the sorbitan esters is comprised mainly of natural fatty acids (e.g., lauric, stearic and oleic acids). The chemical commonality of the sorbitan substructure justifies grouping the six HPV substances together under Group D. Four of the HPV substances are sorbitan monoesters and two have multiple ester linkages (i.e., sorbitan sesquioleate and sorbitan trioleate). The sorbitan esters on the HPV list covered the C18-C60 carbon number range and contained fatty acids in the C6-C18 carbon number range. Three of the substances (i.e., oleate esters of sorbitan) are essentially the same, exception for the degree of esterification.

Sorbitan esters are non-ionic surfactant-active agents that typically find use as emulsifiers, stabilizers, and thickeners in foods, cosmetics, medical products, lubrication and other applications. Many of the HPV sorbitan esters have widespread use in cosmetic and pharmaceutical applications. More importantly, there exist an extensive database of toxicity and health safety information for many of these sorbitan esters (Elder, 1985a; CIR, 1999). Based on the chemical similarity among the HPV sorbitan esters and the toxicity data available for sorbitan stearate, oleate and laurate, and other tested substances, there are sufficient data to cover the majority of the carbon numbers in this group. The chemical structural similarities between HPV sorbitan esters permit "read-across" assessments and support the scientific justification for bridging data gaps for toxicity endpoints for the less-studied members of this group.

Physicochemical properties and environmental fate information are provided in Table 2D. A summary of the available toxicology data is shown in Table 3D. No additional testing is proposed for Group D.

Group D	Acute	Repeat dose	Genetic tox (mutation)	Genetic tox (chrom ab)	Reprod	Develop	Acute fish	Acute daphnia	Algal	Biodeg
Sorbitan monolaurate	√	√	R	R	TD	TD	√	R	R	√
Fatty acids, coco, monoesters with sorbitan	R	R	R	R	TD	TD	R	R	R	R
Sorbitan monostearate	√	√	√	√	TD	TD	R	R	R	R
Sorbitan monoleate	√	√	R	R	TD	TD	√	R	R	√
Sorbitan sesquioleate	√	R	R	R	TD	TD	R	R	R	R
Sorbitan, fatty acids C6-10 tetraester *	√	√	√	R	TD	TD	√	√	√	√
Sorbitan trioleate	√	R	R	R	TD	TD	R	R	R	R

* Not U.S. HPV aliphatic ester; data included for read-across to other group category members
Abbreviations in table: √ = adequate data; R = read-across, TD = Technical Discussion Proposed

Group E - Aliphatic Esters, comprised of Monoacids and Trihydroxy or Polyhydrol Alcohols - "Polyol Esters"

Fifteen HPV aliphatic esters were organized into Group E. These substances are structurally related "polyol esters" derived from common fatty acids, ranging from C5-C18 in carbon number and often containing natural fatty acids (e.g., oleic, stearic acid). The distinguishing "polyol" portion of the ester molecule consists of either:

- Pentaerythritol (PE),
- Trimethylolpropane (TMP) or 2-ethyl-2-(hydroxymethyl)-1,3-propanediol, or
- Dipentaerythritol (diPE).

Since multiple hydroxy groups are present in these polyols (see Section 2.3 for structures), Group E esters may have multiple ester linkages and may include mixed esters having different carbon-length fatty acids. Seven other polyol esters, which are not on the HPV list, were also reviewed because they were chemically similar and provided useful data for bridging the toxicity of substances in this group.

These seven non-HPV polyol esters are:

- TMP ester of heptanoic and octanoic acid,
- Heptanoic acid ester with TMP (CAS 71839-38-8),
- Hexanedioic acid, mixed esters with C9-C11 alcohols and TMP (CAS 180788-27-6),
- Hexanedioic acid, mixed esters with heptanoic, octanoic and decanoic acid and PE (CAS 68130-55-2),
- Fatty acids, C5-C9, esters with PE,
- Fatty acids, C6-C10, tetraester with PE, and
- Fatty acids, C5-C9, esters with dipentaerythritol

Physicochemical Properties

The physicochemical properties for the fifteen esters were either determined experimentally or were calculated using EPIWIN and are summarized in Table 2E. Computer models were also used to estimate these properties for comparison with measured values and to help predict the environmental distribution of the HPV Group E polyol esters.

In general, the polyol esters have molecular weights of greater than 400, have high boiling points greater than >400°C and are expected to be relatively non-volatile, lipophilic (log P > 7) and are relatively water-insoluble.

Hydrolysis half-lives, atmospheric photodegradation rates, and distribution between the environmental compartments for Group E polyol esters were calculated using EPIWIN and are summarized in the Table 2E.

Sufficient physicochemical data exist for the Group E polyol esters and no additional testing is needed.

Mammalian Toxicity

Acute Toxicity. Twelve (12) of the 22 polyol esters in Group E have been adequately tested for acute oral toxicity. The acute oral LD50 for these substances was greater than 2000 mg/kg indicating a relatively low order of toxicity. The similarity in the low order of toxicity for these substances is consistent with their similar chemical structure and physicochemical properties and supports the scientific justification for bridging data gaps. Consequently, no additional acute toxicity testing is proposed.

Repeated Dose Toxicity. The HPV Challenge Program requires that a repeated-dose toxicity study be performed or bridged to structurally related analog compounds. Only limited repeated-dose toxicity data are available for the HPV substances listed in Group E. However, adequate data for repeated-dose toxicity are available for six structurally related non-HPV polyol esters, and no additional testing is proposed.

The HPV substance, TMP ester (C8, C10 acid) (CAS 11138-60-6), was evaluated for repeated dose toxicity in a 28-day dermal study. The effects noted as a result of treatment (viz., decrease in body weight and serum protein values) were slight and of little toxicological concern. There was no evidence of microscopic changes noted in the histopathological evaluation; therefore, the NOAEL for TMP ester (C8, C10 acid) was 2000 mg/kg/day.

Five 28-day oral toxicity studies in rats and one 28-day dermal toxicity study in rats, exist for the following structurally related non-HPV polyol esters [designated **(a)** to **(e)** for discussion in text]:

Repeated-dose Oral Toxicity

(a) TMP esters of heptanoic and octanoic acid
(b) Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol
(c) Hexanedioic acid, mixed esters with C10-rich, C9-11 isoalcohols and TMP
(d) Fatty acid, C6-10, tetraesters with PE
(e) Fatty acid, C6-10, tetraesters with PE

Repeated-dose Dermal Toxicity

(f) Hexanedioic acid mixed esters with decanoic acid, heptanoic acid, octanoic acid and PE

Repeated-dose Oral Toxicity

The non-HPV structurally related polyol esters, **(a)** through **(e)**, were well tolerated by rats in the 28-day oral toxicity studies. The NOAEL for these substances was 1000 mg/kg/day in Sprague-Dawley rats. The non-HPV polyol ester **(a)** (which is TMP ester of heptanoic and octanoic acid), was also well tolerated by rats in a 28-day oral toxicity study. This material did not produce signs of overt systemic toxicity at any dose levels tested (i.e., 100, 300, and 1000 mg/kg/day). There were no treatment-related clinical in-life, functional observation battery, or gross postmortem findings. There were no treatment related mortality, and no adverse effects on body weight, food consumption, clinical laboratory parameters, or organ weights. However, there were increased numbers of hyaline droplets in the proximal cortical tubular epithelium of the 300 and 1000 mg/kg/day in male rats. Based on these findings (hyaline droplets), the NOAEL for the polyol ester **(a)** (i.e., TMP esters of heptanoic and octanoic acid) was established at 100 mg/kg/day for male

rats. Hyaline droplet formation observed in the male kidneys is believed to be a sex/species condition specific to only male rats, which has little relevance to humans.

Repeated-dose Dermal Toxicity

The polyol ester **(f)** (which is hexanedioic acid, mixed esters with decanoic acid, heptanoic acid, octanoic acid and PE) was applied to the skin of groups of 10 (male and female) rats for five days a week for four (4) weeks at dose levels of 0, 125, 500 and 2000 mg/kg/day. Treated animals exhibited no signs indicative of systemic toxicity. No visible signs of irritation were observed at treatment sites. Microscopically, treated skin (viz., greater than or equal to 500 mg/kg/day) exhibited a dose-related increased incidence and severity of hyperplasia and hyperkeratosis of the epidermis and sebaceous gland hyperplasia. These effects were reversible. None of the minor changes in hematology and serum chemistry parameters were considered biologically significant. High dose females (2000 mg/kg/day) exhibited a significant increase in relative adrenal and brain weights when compared to the controls. These differences were attributed to the lower final body weight of the female animals. The NOAEL in this study for systemic toxicity was established as 500 mg /kg/day and 125 mg/kg/day for skin irritation.

Seven repeated-dose toxicity studies using two different routes of administration have been conducted with one HPV listed substance, decanoic acid, ester with 2-ethyl-2-(hydroxy methyl)-1,3-propanediol octanoate (CAS 11138-60-6), and six non-HPV structurally related polyol esters (see Table 3E). The results from these repeated dose toxicity studies suggest that polyol esters exhibit a low order of toxicity following repeated application. This may be attributable to similarities in their chemical structures, physicochemical properties, and common metabolic pathways (i.e., esters can be enzymatically hydrolyzed to the corrresponding polyalcohol and the corresponding fatty acids) which would support scientific justification for using the matrix set of toxicity information for bridging data gaps within Group E. Hence, by bridging these data, the polyol esters have been evaluated adequately for repeated exposure toxicity, and no additional testing is proposed for Group E.

Genetic Toxicity (Salmonella). The majority of the HPV and non-HPV substances in Group E (11 of 22 substances) have been adequately tested for genetic activity in the Salmonella assay, and all were inactive. This suggests that all the polyol esters and structural analogs lack genetic activity due to their similarity in chemical structure and physicochemical properties and support scientific justification for bridging data gaps. Consequently, no additional point mutation assays in bacterial cells or mammalian cells are proposed for substances in this group.

Chromosomal Aberrations. Seven (7) representative members of the polyol esters group have been adequately tested for chromosomal mutation in the *in vitro* mammalian chromosome aberration assay, and all were inactive. Two TMP esters were also tested for *in vivo* chromosomal aberration in rats, and both demonstrated no activity. Thus, it is unlikely that these substances are chromosomal mutagens. No further genotoxicity testing for chromosomal aberrations is proposed for the Group E polyol esters.

Toxicity to reproduction. The HPV listed substance, decanoic acid, ester with 2-ethyl-2-(hydroxy methyl)-1,3-propanediol octanoate (CAS 11138-60-6) (which is a TMP ester with C8, C10 acid) was evaluated for reproductive/developmental toxicity. According to the sponsor of the study, the test material showed no reproductive/developmental effects. Negotiations are underway in order to obtain a copy of the final report. No other reproductive toxicity studies have been conducted with polyol esters; however, no adverse effects to reproductive tissues were observed in the repeated dose toxicity studies. Since metabolism of the polyol esters can occur, leading to the generation of the corresponding fatty acids and the polyol alcohol (such as pentaerthyritol, trimethylolpropane, and dipentaerythritol), the issue of whether these metabolites may pose any potential reproductive/developmental toxicity concerns is important to address. However, the polyol alcohols such as pentaerthyritol, trimethylolpropane, and dipentaerythritol, would be expected to undergo further metabolism, conjugation and excretion in the urine. Available evidence indicates that these ester hydrolysates (i.e., hydrolysis products), primarily fatty acids (e.g., heptanoic, octanoic, and decanoic acids; see Cragg, 2001a) and secondarily the polyol alcohols should exhibit a low order of reproductive toxicity. A technical discussion document is proposed to address any potential reproductive toxicity concerns of polyol esters. Thus, it can be concluded that this group of high molecular weight polyol esters should not produce profound reproductive effects in rodents and no further testing of substances is warranted.

Developmental Toxicity. The HPV listed substance, decanoic acid, ester with 2-ethyl-2-(hydroxy methyl)-1,3-propanediol octanoate (CAS 11138-60-6) (which is a TMP ester with C8, C10 acid) was evaluated for reproductive/developmental toxicity. According to the sponsor of the study, the test material showed no reproductive/developmental effects. Negotiations are underway in order to obtain a copy of the final report. No other developmental toxicity studies have been conducted with polyol esters. Since metabolism of the polyol esters can occur, leading to the generation of the corresponding fatty acids and the polyol alcohol (such as pentaerthyritol, trimethylolpropane, and dipentaerythritol), the issue of whether these metabolites may pose any potential reproductive/developmental toxicity concerns is important to address. However, the polyol alcohols such as pentaerthyritol, trimethylolpropane, and dipentaerythritol, would be expected to undergo further metabolism, conjugation and excretion in the urine. Available evidence indicates that these ester hydrolysates, primarily fatty acids (e.g., heptanoic, octanoic, and decanoic acids; see Cragg, 2001a) and secondarily the polyol alcohols should exhibit a low order of reproductive/developmental toxicity. A technical discussion is proposed to address any potential developmental toxicity concerns of polyol esters. Thus, it can be concluded that this group of high molecular weight polyol esters should not cause fetal toxicity and developmental anomalies in rodents and no further testing of substances is warranted.

Environmental Toxicity and Biodegradation

Acute aquatic toxicity studies have been carried out for most of the HPV polyol esters and the non-HPV polyol esters. There is sufficient information on the aquatic toxicity of many of the Group E polyol esters in fish, invertebrates and algae (Table 3E). In general, the tested polyol esters do not cause acute toxicity to aquatic organisms. In addition, polyol esters have very limited water solubility and these materials are probably not likely to cause toxicity at their maximum water solubility. The matrix set of available aquatic toxicity data provides adequate information for read-across assessment and for bridging the toxicity data gaps for polyol esters. For these reasons, no additional aquatic toxicity testing is necessary for substances in this group.

Biodegradability results have been reported for seven of the 15 HPV polyol esters as well as four of the seven non-HPV polyol esters (see Table 3E). All of the tested polyol esters showed extensive biodegradation in the standard 28-day test and these findings indicate that polyol esters are capable of undergoing metabolic ester cleavage, which leads to the generation of the corresponding fatty acids as well as the polyol alcohols.

Interestingly, the "readily" biodegradability findings observed for some polyol esters (especially pentaerythritol esters and those with natural fatty acids such as oleic acid) indicate that enzymatic cleavage of the ester linkage(s) must be occurring significantly, in order to achieve the high level of biodegradation observed. This would be consistent with the fact that fatty acids (e.g., oleic acids), arising from enzymatic cleavage of the polyol esters, are rapidly biodegraded (Vershueren, 1996; Swisher, 1987). In addition, the results are also consistent with the fact the pentaerythritol itself is readily biodegradable (84% biodegradation in 28 days) (Birch et al. 1991). Thus, there is sufficient biodegradability information available from the matrix set of HPV and non-HPV substances to provide useful data for "read-across" for other polyol esters in Group E, based on chemical similarities, type of polyol ester and fatty acids. For these reasons, the dataset available for the polyol esters is considered adequate to address the biodegradability of the HPV polyol esters, and hence, no additional biodegradation tests are proposed for substances in Group E.

Overview

As discussed earlier, fifteen HPV polyol esters were organized into Group E. These substances were grouped together since they represented structurally related "polyol esters" which are comprised of fatty acids that are linked to one of the multiple hydroxyl groups of the polyol. The polyol molecule can be pentaerythritol (PE), trimethylolpropane (TMP) or dipentaerythritol (diPE). The fatty acids can range from C5-C18 in carbon number and often contain the natural fatty acids, oleic and stearic acids. The fifteen HPV polyol esters fall in the C24-C77 carbon range; for this reason, most of the polyol esters have high boiling points, low volatility, low water-solubility and high lipophilic characteristics.

Seven other non-HPV polyol esters, especially TMP esters of heptanoic and octanoic acid; heptanoic acid ester with TMP (CAS 71839-38-8); hexanedioic acid, mixed esters with C9-C11 alcohols and TMP (CAS 180788-27-6); hexanedioic acid, mixed esters with heptanoic, octanoic and decanoic acid and PE (CAS 68130-55-2); and fatty acids, C6-C10, tetraester with PE, have been extensively tested (Table 3E). They are included in this review mainly because they provide useful toxicological data for assessing the Group E substances.

The chemical structure similarities among the polyol esters support scientific justification for bridging data gaps within this group. The physicochemical, environmental and toxicological data

from the HPV and the non-HPV materials cover the majority of carbon numbers in the polyol esters within this group.

Physicochemical properties and environmental fate information are provided in Table 2E. A summary of the available toxicology data is shown in Table 3E. No additional testing is proposed for Group E.

Group E Name (Type Ester; Acids)	Acute	Repeat dose	Genetic tox (mutation.)	Genetic tox (chrom aber.)	Reprod	Develop	Acute fish	Acute daphnia	Algal	Biodeg
Decanoic acid, mixed esters with heptanoic acid, octanoic acid and trimethylolpropane (TMP Ester; C7, 8, 10 Acid)	R	R	R	R	TD	TD	R	R	R	R
Trimethylolpropane esters of heptanoic and octanoic acid (TMP Ester; C7,8 acid) *	√	√	√	√	TD	TD	√	√	√	√
Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (TMP Ester; C7 acid)*	√	√	√	√	TD	TD	√	R	R	√
Hexanedioic acid, mixed esters with C10-rich, C9-11 isoalcohols and TMP (TMP+C10+iso-C9-11 Alcohols, Mixed Ester, with C6-dioic acid)*	√	√	√	√	TD	TD	√	√	√	√
Decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate (TMP Ester; C8, C10 acids)	√	√	√	√	√	√	√	√	√	√
Nonanoic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP Triester; C9 acid)	√	R	R	√	TD	TD	√	√	√	√
Fatty acids, C14-18 and C16-18 unsatd, triesters with trimethylolpropane (TMP Triester; C14-18 satd,C16-18 unsatd acid)	R	R	R	R	TD	TD	R	R	R	R
9-Octadecenoic acid (Z)-, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP monoester; oleic C18 acid)	√	R	R	R	TD	TD	√	R	R	√
9-Octadecenoic acid (Z)-,2-ethyl-2-[(1-oxo-9-octadecenyl)oxy]methyl]-1,3-propanediyl esterZ (TMP diester; oleic C18 acid)	R	R	R	R	TD	TD	R	R	R	√
Carboxylic acids, C5-9, tetraesters with pentaerythritol (PE tetra ester; C5-9 acids)	√	R	√	R	TD	TD	√	R	R	√
Decanoic acid, mixed esters with heptanoic acid, isovaleric acid, octanoic acid and pentaerythritol (PE mixed esters; C7-8, 10 acids)	R	R	R	R	TD	TD	R	R	R	R
Fatty acids, C5-10, esters with pentaerythritol (PE esters, C5-10 acids)	R	R	R	R	TD	TD	R	R	√	R
Hexanedioic acid mixed esters with decanoic acid, heptanoic acid, octanoic acid and PE (PE Mixed Ester; C6,7,8,10 acids)*	√	√	√	√	TD	TD	√	√	√	√
Nonanoic acid, neopentanetetrayl ester (PE Tetraester; C9 acids)	R	R	R	R	TD	TD	R	R	R	R
Pentaerythritrol, tetrastearate (PE Tetraester; C18 acids	R	R	R	R	TD	TD	R	R	R	R
Fatty acids, C5-9, esters with pentaerythritol (PE Esters; C5-9 acids)*	√	R	√	R	TD	TD	R	R	R	R
Fatty acid, C6-10, tetraesters with PE (PE Tetraester; C9-10 acids)*	√	√	√	√	TD	TD	√	√	√	√
Linseed oil, ester with pentaerythritol (PE ester; oleic, linoleic, linolenic C18 acids)	√	R	R	R	TD	TD	R	R	R	R
Fatty acids, tall oil, tetra esters with pentaerythritol (PE tetraester; oleic, linoleic, C18 acids)	R	R	R	R	TD	TD	R	R	R	R
Fatty acids, C5-10, esters with dipentaerythritol DiPE hexaester; C5-10 acids	√	R	R	R	TD	TD	R	R	√	R
Fatty acids, C5-10, esters with dipentaerythritol DiPE hexaester; C5-9 acids	√	R	√	R	TD	TD	√	R	R	√
Fatty acids, C5-9, esters with dipentaerythritol (diPE Ester; C5-9 acids)*	√	R	√	R	TD	TD	R	R	R	R

*Not U.S. HPV aliphatic ester; data included for read-across to other category members.

√ = adequate data; R = read-across; R = read-across; TD = Technical Discussion proposed

5.0 TEST PLAN SUMMARY

The American Chemistry Council's Aliphatic Esters Panel believes that sufficient health effects and toxicity data exist for the aliphatic esters (and for structurally related and analogous chemicals) to substantially characterize the human health effects, aquatic toxicity and biodegradation endpoints for all the members of this chemical category under the HPV program. No additional toxicity tests are proposed for the aliphatic esters as a chemical category.

The following technical discussions will be developed to complete the health hazard assessments for genetic toxicity (chromosomal aberrations) and for reproductive and/or developmental toxicity endpoints of select groups as noted in Section 4. These include:

- Prepare a technical discussion to explain why Group A monoesters are not likely to cause chromosomal aberration based on their non-reactive and non-electrophilic character and their inherent chemistry.
- Prepare a technical discussion to highlight why glycol esters are not expected to be metabolized in the same manner as polyethylene glycol ethers to methoxyethanol or ethoxyethanol and as a result, account for why the glycol esters in Group C are not likely to cause reproductive/developmental toxicity concerns in the same way as the polyethylene glycol ethers.
- Prepare a technical discussion to explain why the Group D sorbitan esters are not likely to cause reproductive and developmental toxicity in rodents based on the findings that sorbitan monostearate does not cause effects on fertility or gestation in 2-year feeding studies, and based on the multigeneration feeding and teratology studies that showed no reproductive or developmental toxicity for sorbitol.
- Prepare a technical discussion to address the reproductive/developmental toxicity potential of Group E polyol esters and its constituent free polyols and free fatty acids, that may arise from metabolism. Unpublished data indicate that polyol esters such as the TMP mixed ester of octanoic and decanoic acid (CAS 11138-60-6) do not cause reproductive or developmental toxicity in rodents. The discussion will address these findings as well as the low order of toxicity associated with the free polyols and constituent free fatty acids.

For the physicochemical properties and fugacity transport endpoints, the following modeling technical discussion will be developed:

- Calculate physicochemical data and fugacity transport data for the seven non-HPV reference chemicals in Group E, which were used as reference compounds in the matrix data analysis and in read-across assessments to bridge toxicity data gaps in this group. Appropriate QSAR models (e.g., EPIWIN and EQC) will be used to calculate these values which will be supplemented with measured data, if available.

Robust summaries of existing health effects, environmental fate and effects, and physicochemical properties data are attached in the Appendices. In summary, the extensive data available and the test plan described in Section 4, along with the technical discussions, will provide adequate information to substantially and adequately characterize the human health effects, physicochemical properties and environmental fate and effects endpoints for the aliphatic esters under the HPV Chemical Challenge Program.

6.0 REFERENCES *

Andersen FA (1999). Special report: reproductive and developmental toxicity of ethylene glycol and its ethers. Internat. J. Toxicol. 18 (Suppl. 2): 53-67. Comments on polyethylene glycol di-esters on page 65.

Atlas Chemical Industries (ACI) (1970). Summaries of toxicological data. Lifespan feeding studies on sorbitan monolaurate and sorbitan mono-oleate. Food Cosmet. Toxicol. 8: 339-340 (1970) . Summary of data from Toxicology Report on Span 20 and Span 80 (ACI Studies).

Bevan C (2001a). Monohydric Alcohols - C1 to C6 *in* Patty's Toxicology, 5th edition, Bingham E et al. (eds.), Vol. 6, Chapter 77, pp. 365-460. J. Wiley & Sons, New York.

Bevan C (2001b). Monohydric Alcohols - C7 to C18, Aromatic and other alcohols. *in* Patty's Toxicology, 5th edition, Bingham E et al. (eds.), Vol. 6, Chapter 78, pp. 461-541. J. Wiley & Sons, New York.

BIBRA (1987). Toxicity profile for 1,1,1-trimethylolpropane. British Industrial Biological Research Association (BIBRA).

BIBRA (1990). Toxicity profile for 2-ethyl-1-hexanol. British Industrial Biological Research Associaton (BIBRA).

BIBRA (1996). Toxicity profile for di(2-ethylhexyl) sebacate. British Industrial Biological Research Association (BIBRA).

Birch RR, Fletcher RJ (1991). The application of dissolved inorganic carbon measurements to the study of aerobic biodegradability. Chemosphere 23: 855-872.

Bisesi MS (2001). Esters of mono- and alkenyl carboxyulic acids and mono- and polyalcohols *in* Patty's Toxicology, 5th edition, Bingham E et al. (eds.), Vol. 6, Chapter 80, pp. 635-932, J. Wiley & Sons, New York

Cater BR, Butterworth KR, Gaunt IF, Hoosan J, Grasso P and Gangoli SD (1978). Short-term toxicity study of sorbitan monolaurate (Span 20) in rats. Food Cosmet. Toxicol. 16: 519-526.

Cavender FL, Sowinski EJ (2001). Glycols *in* Patty's Toxicology, 5th edition, Bingham E, et al. (eds.), Vol. 7, Chapter 85, pp. 1-71. J. Wiley & Sons, New York.

Chow CK (1999). Biological and toxicological properties of fatty acids and derivatives *in* Fatty Acids in Industry: Process, Properties, Derivatives, Applications. Johnson RW, Fritz E (eds.), Marcel Dekker, New York, pp. 617-658.

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* The list of references is not a comprehensive bibliography of all the aliphatic ester literature. Pertinent papers cited in the text are those that are important in health hazard assessments or in bridging toxicity gaps for structurally similar esters in the various group subcategories. The information and data in the papers and reviews supplement the robust summaries developed for the toxicology studies of the HPV substances, which are ultimately used to address the SIDS toxicity endpoints for the HPV aliphatic esters.

CIR (Cosmetic Ingredient Review) (1999). Final Report Addendum. Safety assessment of sorbitan caprylate, sorbitan cocoate, sorbitan diisostearate, sorbitan dioleate, sorbitan distearate, sorbitan isostearate, sorbitan olivate, sorbitan sesquiisostearate, sorbitan sesquioleate, and sorbitan tiisostearate. Cosmetic Ingredient Review. Washington, DC (1999). June 14, 1999, pp. 1-28.

Cragg ST (2001a). Aliphatic carboxylic acids, saturated *in* Patty's Toxicology, 5th edition, Bingham E, et al. (eds.), Vol. 5, Chapter 70, pp. 689-787. J. Wiley & Sons, New York.

Cragg ST (2001b). Aliphatic carboxylic acids, unsaturated *in* Patty's Toxicology, 5th edition, Bingham E, et al. (eds.), Vol. 5, Chapter 71, pp. 789-861. J. Wiley & Sons, New York.

David RM, McKee RH, Butala JH, Barter RA, Kayser M (2001). Esters of aromatic mono-, di-, and tricarboxylic acids, aromatic diacids and di-, tri- and polyalcohols *in* Patty's Toxicology, 5th edition, Bingham E, et al. (eds.), Vol. 6, Chapter 79, pp. 543-633. J. Wiley & Sons, New York.

Eisenhard WC (1999). Esterification *in* Fatty Acids in Industry: Process, Properties, Derivatives, Applications. Johnson RW, Fritz E (eds.), Marcel Dekker, New York, pp. 139-152.

Elder RL (1982a). Final report on the safety assessment of octyl palmitate, cetyl palmitate and isopropyl palmitate, J. Amer. Coll. Toxicol. 1(2): 13-35.

Elder RL (1982b). Final report on the safety assessment of decyl and isodecyl oleates, J. Amer. Coll. Toxicol. 1(2): 85-95.

Elder RL (1982c). Final report on the safety assessment of glycol stearate, glycol stearate SE and glycol distearate. J. Amer. Coll. Toxicol. 1(2): 1-12.

Elder RL (1983). Final report on the safety assessment of propylene glycol stearate and propylene glycol stearate self-emulsifying. J. Amer. Coll. Toxicol. 2(5): 101-123.

Elder RL (1985a). Final report on the safety assessment of sorbitan stearate, sorbitan laurate, sorbitan sesquioleate, sorbitan trioleate, sorbitan tristearate, sorbitan palmitate and sorbitan trioleate. J. Amer. Coll. Toxicol. 4(3): 65-121.

Elder RL (1985b). Final report on the safety assessment of butyl stearate, cetyl stearate, isobutyl stearate, isopropyl stearate, myristyl stearate and octyl stearate , J. Amer. Coll. Toxicol. 4(5): 107-146.

EPIWIN (1999). Estimation Program Interface for Windows. Version 3.02. Syracuse Research Corp., Syracuse, New York, USA.

Hardman J, Limbard LE, Goodman-Gilman A (eds.) (2001). Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th Ed., McGraw Hill, pp. 1887-1888, Propylene glycol.

Hendy RJ, Butterworth KR, Gaunt IF, Kiss IS, Grasso P (1978). Long-term toxicity study of sorbitan monostearate (Span 60) in mice. Food Cosmet Toxicol. 16: 527-534.

Heyman E (1982). Hydrolysis of carboxylic esters and amides in Metabolic Basis of Detoxification (Jakoby WB, Bend JR, Caldwell J (eds.), Academic Press, New York, pp.229-245

High Production Volume (HPV) (2001). See HPV chemical categories (e.g., dicarboxylic acids, alkyl alcohols C6-C13 categories) submitted to U.S. EPA.

ICI (1988a). ICI Central Toxicology Laboratory. Di-(2-ethylhexyl)adipate (DEHA): Fertility study in the rat. Report CTL/P/2229.

ICI (1988b). ICI Central Toxicology Laboratory. Di-(2-ethylhexyl)adipate (DEHA): Teratogencity study in the rat. Report CTL/P/2119.

Ingram AJ, Butterworth KR, Gaunt IF, Grasso P and Gangoli SD (1978). Short-term toxicity study of sorbitan mono-oleate (Span 80) in rats. Food Cosmet. Toxicol. 16: 535-542.

IUCLID (1996). International Union Chemical Information Database, European Chemicals Bureau Existing Chemicals. Data hedset for each chemical found by CAS number or chemical name.

Johnson W (1999). Final report on the safety assessment of polypropylene glycol (PG) dicaprylate, PG dicaprylate/dicaprate, PG dicocoate, PG dipelargonate, PG isostearate, PG laurate, PG myristate, PG oleate, PG oleate SE, PG dioleate, PG dicaprate, PG diisostearate and PG dilaurate. Internat. J. Toxicol. 18 (Suppl. 2): 35-52.

Klimisch H, Andreae M, Tillman U (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. 15: 1-5.

Letinski DJ, Connelly MJ, Petersen DR, Parkerton TF (2001). Slow-stir measurements of selected alcohols and diesters. Chemosphere (manuscript submitted).

MacKensie KM, Hauck WN, Wheeler AG, Roe FJC (1986). Three-generation reproduction study of rats ingesting up to 10% sorbitol in the diet - and a brief review of the toxicological status of sorbitol. Food Chem. Toxicol. 24: 191-200.

Mackay D, DiGuardo A, Paterson S, Cowan CE (1996). Evaluating the environmental fate of a variety of types of chemicals using the EQC model. Environ. Toxicol. Chem. 15: 1627-1637.

Modderman JP (1993). Safety assessment of hydrogenated starch hydrolysates. Regul. Toxicol. Pharmacol. 18: 80-114.

Monick JA (1968). Alcohols: Their Chemistry, Properties and Manufacture. Reinhold Book Corp., New York.

Munro IC, Kennepohl E (2001). Comparison of estimated daily per capita intakes of flavouring substances with no-observed-effect levels from animal studies. Food Chem. Toxicol. 39: 331-354.

Oser BL, Oser M (1956). Nutritional studies on the diets containing high levels of partial ester emulsifiers. II. Reproduction and lactation . J. Nutrit. 60: 489-505.

Oser BL, Oser M (1957). Nutritional studies on the diets containing high levels of partial ester emulsifiers. IV. Mortality and post-mortem pathology: general conclusions. J. Nutrit. 61: 235.

Parkinson A (2001). Biotransfromation of xenobiotics: (hydrolysis) in Casarett & Doull's Toxicology: The Basic Science of Poisons (Klassen CD, ed.), McGraw-Hill, New York, pp. 137-142.

Patty's Toxicology, 5th edition. Bingham E, Cohrssen B, Powell C (editors). 8-Volumes. J. Wiley & Sons, New York (2001).

Proctor and Hughes (1996). Proctor and Hughes Chemical Hazards at the Workplace (4th Edition), Van Nostrand Reinhold, New York.

Randles SJ (1999). Esters *in* Synthetic Lubricants and High Performance Functional Fluids (2nd ed.), Rudnick LR and Shubkin RL (eds.), Marcel Dekker, New York, pp. 63-101.

Reck RA (1999). Polyoxyethylene esters of fatty acids in *in* Fatty Acids in Industry: Process, Properties, Derivatives, Applications. Johnson RW, Fritz E (eds.), Marcel Dekker, New York, pp. 201-216.

RTECS (Registry of Toxic Effects of Chemical Substances (2001). National Institute for Occupational Safety and Health of the U.S. Department of Health and Human Services. Health hazard and toxicity data for individual chemical was found by CAS number or chemical name.

Satoh T, Hosokawa M. (1998). The mammalian carboxylesterases: from molecules to functions. Ann. Rev. Toxico. Pharmacol. 38: 257-288.

Snyder R. (Year). Ethel Browning's Toxicity and Metabolism of Industrial Solvents. Elsevier, New York.

Swisher RD (1987). Surfactant Biodegradation (2nd ed.), Marcel Dekker, New York, pp. 728-729; 826-827.

Thurman RG, Kauffman FC (eds.)(1992). Alcohols and Esters. Volume 3 in Ethel Browning's Toxicity and Metabolism of Industrial Solvents (2nd Ed.), Snyder R (Series Editor), Elsevier, Amsterdam.

U.S. EPA (1999). Determining the adequacy of existing data. OPPT, EPA.

U.S. EPA (1999). The use of structure-activity relationships (SAR) in the High Production Volume (HPV) Chemical Challenge Program. OPPT. EPA.

Verschueren K (1996). Handbook of Environmental Data on Organic Chemicals (3rd ed.), Wiley, New York.

Von Oettingen WF (1960). The aliphatic acids and their esters: toxicity and potential dangers, the saturated monobasic acids and their esters; aliphatic acids with three to eighteen carbons and their esters. AMA Arch. Ind. Health. 21: 100-113.

7.0 List of Tables and Figures

Table 2A. Group A - Aliphatic Esters, comprised of Monoacids and Monoalcohols
Summary Table of Physicochemical Data for "Monoesters"

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	MP* (°C)	BP** (°C)	Vapor Pressure (Pa@25°C)	Octanol-Water Partition Coefficient (log Pow)	Water Solubility (mg/L @25°C)	Photo-degradation Half-life (days)	Hydrolysis Half-life (yrs)	Transport (%) c			
											Soil	Air	Water	Sediment
22	341	123-95-5	Stearic acid, butyl ester	26-27 109 c	343 384 c	1.27 E-05 (20) 8.1 E-04 c	9.7 c	3.6 E-05 c	0.411 c	9.09 c	27.8	0.07	7.25	64.3
24	369	29806-73-3	Palmitic acid, 2-ethylhexyl ester	117 c	400 c	1.02 E-06 c	10.6 c	4.13 E-06 c	0.36 c	14.1 c	28.3	0.57	7.2	63.9
26	393-395	68334-13-4	Fatty acids, tall oil, 2-ethylhexyl ester	114 c	427 c	1.98 E-05 c	11.4 c	6.3 E-07 c	0.056 c	0.056 l/mol s c	28	0.5-0.9	7.3	64-69
26	397	85049-37-2	Fatty Acids, C16-18 satd and C18 unsatd, 2-ethylhexyl ester	135 c	423 c	1.76 E-07 c	11.6 c	4.02 E-07 c	0.331 c	14.1 c	29.1	0.1	7.1	63.3
26	397	109-36-4	Stearic acid, octyl ester	145 c	430 c	9.28 E-08c	11.67 c	3.48 E-07c	0.34 c	20.4 c	29.5	0.48	7.09	62.9
28	423	3687-46-5	Oleic acid, decyl ester	161 c	457 c	1.31 E-08c	12.44 c	5.3 E-08 c	0.12 c	20.4 c	28.5	0.09	7.23	64.2
31	467	31556-45-3	Stearic acid, tridecyl ester	190 c	488 c	1.40 E-07 c	14.1 c	1.0 E-09 c	0.28 c	20.4 c	30.9	0.35	7.0	61.8
32	481	17661-50-6	Stearic acid, myristyl ester	54 192 c	500 c	1.5 E-08 c	14.6 c	3.13 E-10 c	0.27 c	20.4 c	29.8	0.38	7.07	62.8
34	494	25339-09-7	Stearic acid, isocetyl ester	207 c	516 c	1.25 E-10 c	15.52 c	3.47 E-11 c	0.25 c	20.4 c	30	0.13	3.4	66.6

Highlighted rows are not on the HPV list but included to facilitate category evaluation

c = calculated data using EPWIN; all other values are derived from measurements

* = Note: Mixtures are expected to have melting points below those of pure components. Modeled data do not accurately reflect melting points for these substances.

** = boiling points for some esters may have been determined under reduced pressure.

Table 2B. Group B - Aliphatic Esters, comprised of Diacids and Monoalcohols
Summary Table of Physicochemical Data for "Diesters" (e.g., Adipates, Maleates, Azelates, Sebacates)

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	MP* (°C)	BP** (°C)	Vapor Pressure (Pa@25°C)	Octanol-Water Partition Coefficient (log Pow)	Water Solubility (mg/L @25°C)	Photo-degradation Half-life (days)	Hydrolysis Half-life (yrs)	Transport (%) c			
											Soil	Air	Water	Sediment
12	228	105-76-0	Maleic acid, dibutylester	< -60 -28 c	277-288 267 c	<1 E-02 hPa 5.32 E-03 c	3.38 4.16 c	173 (20 C) 8.7 c	0.33 c	0.33 0.33 c	55.9	2.7	39.3	2.2
16	284	105-52-2	Maleic acid, bis(1,3-dimethylbutyl)ester	-28 c	292 c	0.0297 c	5.8 c	0.16 c	0.23 c	12.2 c	37.3	0.9	16.4	45.3
20	341	142-16-5	Maleic acid, bis(2-ethylhexyl)ester	-60 pour pt 29 c	164 (10mmHg) 360 c	7.2 E-05 c	7.9 c	0.00117 c	0.19 c	0.52 c	29.6	1.1	11.2	58.1
12	230	6938-94-9	Adipic acid, diisopropyl ester	-1 -48 c	120 (6.5 mmHg) 136 (14 mm Hg) 241 c	0.0446 c	3.2 c	55.6 c	1.03 c	2.33 c	58.8	2.7	38	0.6
14	258	105-99-7	Adipic acid, dibutyl ester	-11 -6.6 c	294 c	0.00273 c	4.33 c	4.2 c	0.84 c	2.07 c	54	3.6	39.3	3.1
21	356	68515-75-3	Adipic acid, di-C7-9 branched and linear alkyl esters	< 0 30 c	361 c	8.89 E-03 c	7.55 c	0.0020 c	0.45 c	3.21 c	27.3	0.3	3.6	68.8
22	370	1330-86-5	Adipic acid, diisooctyl ester	-70 9 c	>300 379 c	3.53 E-03 c	8.12 c	5.45 E-04 c	0.45 c	2.07 c	27.3	0.3	3.5	69
22	370	108-63-4	Adipic acid, bis(1-methylheptyl) ester	9 c	175 (2 mmHg) 379 c	2.65 E-05 c	8.1 c	0.00545 c	0.42 c	2.33 c	29.5	1.2	11.1	58.2
22	370	103-23-1	Adipic acid, bis(2-ethylhexyl) ester	-79 9 c	417 379 c	6.3 E-05 3.5 E-05 c	8.12 c	3.2 E-03 (1) 5.45 E-04 c	0.40 c	3.2 c	31.4	1.0	10.8	56.8
22	435	141-17-3	Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester	117 c	441 c	9.84 E-08 c	3.2 c	3.2 c	0.15 c	0.81 c	71.7	0	27.8	0.4
24	399	33703-08-1	Adipic acid, diisononyl ester	< -60 56 c	> 300 416 c	0.9 (200 mgHg) 2.25 E-04 c	9.24 c	2.2 E-04 (1) 3.98 E-05 c	0.40 c	4.64 c	28.8	0.6	7.2	63.4
26	427	27178-16-1	Adipic acid, diisodecyl ester	< -60 51 c	> 300 426 c	1.69 E-06 1.51 E-04 c	10.1 c	4.4 E-05 (1) 5.15 E-06 c	0.36 c	2.07 c	28.5	0.2	3.4	67.9
32	511	16958-92-2	Adipic acid, ditridecyl ester	< 0 141 c	509 c	1.45 E-07 c	13.17 c	3.43 E-09 c	0.28 c	4.64 c	31.0	0.4	7.0	61.7
25	413	103-24-2	Azelaic acid, bis(2-ethylhexyl)ester	-78 41 c	237 (5 mmHg) 414 c	1.66 E-05 c	9.6 c	1.65 E-05 c	0.36 c	3.22 c	28.4	0.6	7.2	63.8
29	469	28472-97-1	Azelaic acid, diisodecyl ester	83 c	460 c	7.61 E-08 c	11.6 c	1.54 E-07 c	0.32 c	2.1 c	29.8	0.2	3.4	66.6
12	230	106-79-6	Sebacic acid, dimethyl ester	38 -27 c	261 c	0.011 c	3.4 c	120 41.7 c	1.1 c	3.6 c	60.1	2.5	36.7	0.7
26	469	122-62-3	Sebacic acid, bis(2-ethylhexyl)ester	51 c	212 (1mm Hg) 426 c	1.97 E-06 c	3.74 10.1 c	1.5 E-07 c	0.35 c	7.1 c	28.7	0.5	7.2	63.6

Highlighted rows are not on the HPV list but included to facilitate group category evaluation

c = calculated data using EPWIN; all other values are derived from measurements

* = Note: Mixtures are expected to have melting points below those of pure components. Modeled data do not accurately reflect melting points for these substances.

** = many of the esters have boiling points determined under reduced pressure and some values have been extrapolated to one atmosphere

(1) Recent water solubility data were determined by the method of D Letinski et al. (2001). Slow-stir water solubility measurements of selected alcohols and diesters (manuscript submitted to Chemosphere)

Table 2C. Group C - Aliphatic Esters, comprised of Monoacids and Dihydroxy Alcohols
Summary Table of Physicochemical Data for "Glycol Esters"

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	MP* (°C)	BP** (°C)	Vapor Pressure (Pa@25°C)	Octanol-Water Partition Coefficient (log Pow)	Water Solubility (mg/L @25°C)	Photo-degradation Half-life (days)	Hydrolysis Half-life (yrs)	Transport (%) c			
											Soil	Air	Water	Sediment
15	258	71839-38-8	Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol	-50 75 c	>300 322 c	2.8 E-05 1.08 E-05 c	>6.3 4.6 c	2.7 7.84 c	0.50 c	10.6 c	58.7	1.1	32.2	7.9
20	329	111-60-4	Stearic acid, 2-hydroxyethyl ester	57-60 138 c	404c	6.58 E-08 c	7.26 c	0.01711 c	0.39 c	7.7 c	31.0	0.5	7.5	61
20	375	7434-40-4	Triethylene glycol, diheptanoate	-24 54 c	>250 (decomp) 394 c	6.29 E-06 c	4.77 c	30 0.3732 c	0.25 c	0.81 c	67.4	0.0	24.3	8.3
21	343	1323-39-3	Propylene glycol, monostearate	132 c	405 c	1.12 E-08 c	7.67 c	0.0062 c	0.34 c	7.7 c	31.3	0.4	7.1	61.2
22	419	70729-68-9	Heptanoic acid, oxybis(2,1-ethanediyloxy-2,1-ethanediyl) ester	94 c	429 c	3.39 E-07 c	2.86 4.49 c	0.3419 c	0.19 c	0.81 c	69.5	0.0	25.7	4.8
23	368	67989-24-6	9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (Monoester)	157 c	431 c	1.01 E-09 c	8.40 c	0.0010 c	0.07 c	6.5 c	28.8	0.1	7.3	63.9
24	431	68583-52-8	Decanoic acid, mixed diesters with octanoic acid and triethylene glycol	96 c	441 c	1.74 E-07 c	6.73 c	0.0035 c	0.22 c	1.1 c	42	0.0	7.3	50.7
24	447	18268-70-7	Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol	89 c	439 c	2.28 E-07 c	5.33 c	0.0441 c	0.18 c	30.8 c	59.7	0.0	19.1	21.2
27	441	22788-19-8	Propylene glycol dilaurate	75 c	444 c	2.31 E-07 c	10.64 c	1.38 E-06 c	0.34 c	5.9 c	30.1	0.5	7.0	62.4
38	595	627-83-8	Stearic acid, ethylene ester (Diester)	79 212 c	189-191** 579 c	8.01 E-11 c	16.12 c	2.97 E-12 c	0.23 c	1.8 c	30.6	0.3	7.0	62.1
39	605	105-62-4	Oleic acid, propylene ester	197 c	591 c	2.0 E-12 c	16.11 c	2.61 E-12 c	0.04 c	0.73 c	27.6	0.0	3.5	68.9
39	609	68958-54-3	Propylene glycol diisostearate	175 c	569 c	1.29 E-11 c	16.39 c	1.41 E-12 c	0.22 c	5.9 c	30.4	0.1	2.3	67.2
41	633	42222-50-4	9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester (Diester)	234 c	609 c	2.38 E-13 c	17.05 c	2.67 E-13 c	0.03 c	3.3 c	27.6	0.0	3.5	68.9

Highlighted rows are not on the HPV list but included to facilitate category evaluation

c = calculated data using EPWIN; all other values are derived from measurements

* = Note: Mixtures are expected to have melting points below those of pure components. Modeled data do not accurately reflect melting points for these substances.

** = boiling points for some esters may have been determined under reduced pressure.

Table 2D. Group D - Aliphatic Esters, comprised of Monoacids and Sorbitan
Summary Table of Physicochemical Data for "Sorbitan Esters"

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	MP* (°C)	BP** (°C)	Vapor Pressure (Pa@25°C)	Octanol-Water Partition Coefficient (log Pow)	Water Solubility (mg/L @25°C)	Photo-degradation Half-life (days)	Hydrolysis Half-life (yrs)	Transport (%) c			
											Soil	Air	Water	Sediment
18	346	1338-39-2	Sorbitan, monolaurate	176 c	462 c	9.34 E-12 c	3.15 c	13.19 c	0.20 c	14.2 c	68.2	0.04	31.4	0.3
18-20	346-374	68154-36-9	Fatty acids, coco, monoesters with sorbitan (main fatty acids are lauric and myristic acids)	176-191 c	462-485 c	1.1-9.3 E-12 c	3.15-4.14 c	1.29-13.2 c	0.19-0.20 c	7.7 - 14.2 c	64.6-68.2	0.04-0.3	31.4-33.4	0.3-1.8
24	431	1338-41-6	Sorbitan, monostearate	222 c	531 c	1.38 E-14 c	6.10 c	0.0122 c	0.17 c	7.7 c	36.2	0.3	12.6	50.9
24	430	1338-43-8	Sorbitan, monooleate	223 c	535 c	1.03 E-14 c	5.89 c	0.0191 c	0.05 c	2.2 c	37.2	0.1	15.6	47.1
33	569	8007-43-0	Sorbitan, sesquioleate	248 c	609 c	6.83 E-17 c	10.11 c	5.93 E-07 c	0.04 c	0.90 c	28.6	0.1	7.2	64.1
38	669	228573-47-5	Sorbitan, Fatty Acid C6-10 Tetraester	< -25C 266 c	>295 C 636 c	1.7 E-07 1.87 E-14 c	>7.7 11.57 c	<0.02 7.37 E-09 c	0.19 c	0.79 c	32.1	0.5	10.7	56.7
60	958	26266-58-0	Sorbitan, trioleate	350 c	916 c	1.32 E-19 c	21.71 c	5.97 E-19 c	0.02 c	0.59 c	27.4	0.0	3.5	69.1

Highlighted rows are not on the HPV list but included to facilitate category evaluation

c = calculated data using EPWIN; all other values are derived from measurements

* = Note: Mixtures are expected to have melting points below those of pure components. Modeled data do not accurately reflect melting points for these substances.

** = boiling points for some esters may have been determined under reduced pressure.

Table 2E. Group E - Aliphatic Esters, comprised of Monoacids and Trihydroxy or Polyhydroxy Alcohols (Polyols) Summary Table of Physicochemical Data for "Polyol Esters" (e.g., TMP, PE and diPE Esters)

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	MP* (°C)	BP** (°C)	Vapor Pressure (Pa@25°C)	Octanol-Water Partition Coefficient (log Pow)	Water Solubility (mg/L @25°C)	Photo-degradation Half-life (days)	Hydrolysis Half-life (yrs)	Transport (%) c			
											Soil	Air	Water	Sediment
31	513	68130-53-0	Decanoic acid, mixed esters with heptanoic acid, octanoic acid and trimethylolpropane (TMP Ester; C7, 8, 10 Acid)	148 c	505 c	1.14 E-09 c	10.68 c	4.52 E-07 c	0.31 c	0.89 c	32.9	0.7	10.5	55.8
24	415	11138-60-6	Decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate (TMP Ester; C8, C10 Acid)	116 c	>300 448 c	< 13 Pa 25C 8.7 E-10 c	>2.7 7.67 c	0.48 0.0023 c	0.40 c	7.3 c	34.7	0.3	6.8	58.2
33	555	126-57-8	Nonanoic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP Triester; C9 Acid)	-16 Pour pt 193 c	>300 535 c	21 Pa 25C 5.86 E-11 c	>2.8 12.11 c	8.4 1.44 E-08 c	0.32 c	7.8 c	31.3	0.4	6.9	61.4
56	875	68002-79-9	Fatty acids, C14-18 and C16-18 unsatd, triesters with trimethylolpropane (TMP Triester; C14-18 satd, C16-18 unsatd Acid)	350 c	806 c	4.4 E-20 c	23.19 c	3.6 E-20 c	0.05 c	4.2 c	27.8	0.03	3.5	68.7
24	417	70024-57-6	9-Octadecenoic acid (Z)-, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP Monoester, Oleic C18 Acid)	228 c	532 c	3.82 E-14 c	6.93 c	0.00728 c	0.19 c	---	31.6	0.3	8.0	60.2
60	928	57675-44-2	9-Octadecenoic acid (Z)-, 2-ethyl-2-[(1-oxo-9-octadecenyl)oxy]methyl]-1,3-propanediyl ester, (Z)- (TMP Diester; Oleic C18 Acid)	350 c	859 c	1.47 E-21 c	24.73 c	7.8 E-22 c	0.02 c	2.2 c	27.4	0.01	3.5	69.1
33	529	67762-53-2	Carboxylic acids, C5-9, tetraesters with pentaerythritol (PE Tetraester; C5-9 Acids)	209 c	522 c	2.83 E-10 c	11.41 c	8.4 E-08 c	0.11 c	----	29.5	0.2	7.1	63.2
37	641	68130-51-8	Decanoic acid, mixed esters with heptanoic acid, isovaleric acid, octanoic acid and pentaerythritol (PE Mixed Ester; C7, 8 Acids)	242 c	601 c	3.12 E-13 c	12.56 c	1.62 -09 c	0.29 c	3.9 c	31.2	0.4	6.9	61.5
	613	68424-31-7	Fatty acids, C5-10, esters with pentaerythritol (PE Ester; C5-10 Acids)	233 c	585 c	1.4 E-10 c	11.7 c	1.5 E-08 c	---	---	34	0.7	11	55
41	697	14450-05-6	Nonanoic acid, neopentanetetrayl ester (PE Tetraester; C9 Acid)	279 c	654 c	4.13 E-15 c	14.6 c	1.25 E-11 c	0.25 c	5.8 c	30.8	0.3	7.0	61.9
77	1202	115-83-3	Pentaerythritrol, tetrastearate (PE Tetraester; C18 Acid)	350 c	1072 c	1.5 E-27 c	32.3 c	3.62 E-30 c	0.12 c	5.8 c	29.4	0.04	2.4	68.2
77	1188	68648-28-2	Linseed oil, ester with pentaerythritol (PE Ester; oleic, linoleic, linolenic C18 acids)	350 c	1097 c	2.87 E-28 c	30.8 c	8.75 E-29 c	0.01 c	1.6 c	27.9	0.0	2.4	69.7
77	1190	68334-18-9	Fatty acids, tall oil, tetra esters with pentaerythritol (PE Tetraester; oleic and linoleic C18 acids)	350c	1094 c	3.63 E-28 c	31.0 c	5.55 E-29 c	0.01 c	1.6 c	27.9	0.0	2.4	69.6
60	927	70983-72-1	Fatty acids, C5-10, esters with dipentaerythritol (DiPE hexaester; C5-10 Acids)	350 c	835 c	9.3 E-19 c	15.8 c	3.6 E-14 c	---	---	34	0.4	11	55
60	955	67762-52-1	Carboxylic acids, C5-9, hexaesters with dipentaerythritol (DiPE hexaesters; C5-C9 Acids)	350 c	858 c	2.1 E-19 c	16.7 c	3.4 E-15 c	---	---	32	0.4	11	57

Highlighted rows are not on the HPV list but included to facilitate category evaluation

c = calculated data using EPWIN; all other values are derived from measurements

* = Note: Mixtures are expected to have melting points below those of pure components. Modeled data do not accurately reflect melting points for these substances.

** = boiling points for some esters may have been determined under reduced pressure.

Table 3A. Group A - Aliphatic Esters, comprised of Monoacids and Monoalcohols - "Monoesters" Summary Table of Toxicology and Biodegradation Data

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Aber.)	Toxicity to Reproduction	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50	Daphnia LC50 or LL50	Algal LC50 or LL50	Biodegradation %
22	341	123-95-5	Stearic acid, butyl ester	>32 g/kg	2-Year Feeding Study (rat) 6.25% in diet showed no significant differences from control animals.			6.25% in diet for 10 weeks in rats showed no effect on fertility, litter size, survival of offspring					
24	369	29806-73-3	Palmitic acid, 2-ethylhexyl ester	>5 g/kg									
26	393-395	68334-13-4	Fatty acids, tall oil, 2-ethylhexyl ester	> 64 g/kg	Read across: (a) 28-day Oral Gavage (rat) NOAEL 1000 mg/kg								
26	397	85049-37-2	Fatty Acids, C16-18 satd and C18 unsatd, 2-ethylhexyl ester	>17.2 g/kg	Read across: (a) 28-day Oral Gavage (rat) NOAEL 1000 mg/kg	Negative (Ames)			Read-Across (b) NOAEL Teratogen > 1000 mg/kg NOAEL Maternal >1000 mg/kg	3200 mg/L	17 mg/L	40-42 mg/L	85% in 28 days OECD 301D Closed Bottle
26	397	109-36-4	Stearic acid, octyl ester	> 8 ml/kg	28-day Oral Gavage (rat) NOAEL 1000 mg/kg	Negative (Ames)			Read-Across (b) NOAEL Teratogen > 1000 mg/kg NOAEL Maternal >1000 mg/kg				
28	423	3687-46-5	Oleic acid, decyl ester	> 40 ml/kg	28-day Oral Gavage (rat) NOAEL 1000 mg/kg	Negative (Ames)				3200 mg/L	17 mg/L	40-42 mg/L	80% in 28 days OECD 301D Closed Bottle
31	467	31556-45-3	Stearic acid, tridecyl ester										
32	481	17661-50-6	Stearic acid, myristyl ester	> 10 g/kg (mice)									
34	494	25339-09-7	Stearic acid, isocetyl ester	> 10 g/kg									

Highlighted rows are not on the HPV list but included to facilitate category evaluation

Footnotes:

a) Read-across for repeated oral toxicity was based on studies with 2-ethylhexyl stearate or octyl stearate, oral gavage rat study at 100, 500 and 1000 mg/kg for 28 days. NOAEL was 1000 mg/kg.

b) Read across for developmental/teratogenicity was based on studies with 2-ethylhexyl ester of C16-18 Fatty acid (CAS 91031-48-0) (IUCLID database, 1996) since structure is very similar to octyl (=2-ethyl hexyl) stearate (CAS 109-34-4) and to Fatty Acid, C16-18 satd and C18 unsatd, 2-ethylhexyl ester (CAS 85049-37-2).

Table 3B. Group B - Aliphatic Esters, comprised of Diacids and Monoalcohols - "Diesters" Summary Table of Toxicology and Biodegradation Data

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Aber.)	Toxicity to Reproduction	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50	Daphnia LC50 or LL50	Algal LC50 or LL50	Biodegradation %
12	228	105-76-0	Maleic acid, dibutyl ester (a)	3.73 g/kg	7-Day Oral gavage study (rat) NOAEL 95 mg/kg/day based on liver and kidney effects	Negative (Ames)	Negative (micronucleus, in vivo, mouse)	Oral gavage study (rat) NOAEL 95 mg/kg/day. No adverse reprod/develop effects on reported	Oral gavage study (rat) NOAEL 95 mg/kg/day. No adverse reprod/develop effects on reported	1.2 mg/L	45 mg/L	6.2 mg/L	Readily Biodeg.
16	284	105-52-2	Maleic acid, bis(1,3-dimethylbutyl)ester	7.46 g/kg									
20	341	142-16-5	Maleic acid, bis(2-ethylhexyl)ester	> 10 ml/kg									
12	230	6938-94-9	Adipic acid, diisopropyl ester	> 15 g/kg (b)									
14	258	105-99-7	Adipic Acid, dibutyl ester	12.9 g/kg									
21	356	68515-75-3	Adipic acid, di-C7-9 branched and linear alkyl esters	>15.8 g/kg	90-Day Oral Diet (rat) NOAEL 1300 mg/kg Male NOAEL 1800 mg/kg Female	Negative (Ames)			Oral Gavage (rat) NOAEL 4000 mg/kg/day (Maternal and developmental)	> 1000 mg/L	1.9 mg/L	1.8-2.5 mg/L	
22	370	1330-86-5	Adipic acid, diisooctyl ester	45.0 g/kg (c)									Readily Biodeg. 86.7% in 28 days OECD 301B
22	370	108-63-4	Adipic acid, bis(1-methylheptyl)ester	> 64 g/kg									
22	370	103-23-1	Adipic acid, bis(2-ethylhexyl)ester	>7380 mg/kg	90-Day Oral (diet) LOAEL (rat) ~600 mg/kg/day; (mouse) ~460 mg/kg/day NOAEL (rat) ~300 mg/kg/day; (mouse) ~230 mg/kg/day	Negative (Ames, mouse lymphoma)	Negative (CHO in vitro; micronucleus, in vivo)	Oral Diet (rat) LOAEL = 1080 mg/kg/day NOAEL = 170 mg/kg/day	Oral Diet (rat) LOAEL = 1080 mg/kg/day NOAEL = 170 mg/kg/day	> 0.1 mg/L (d)	> 500 mg/L (d)	>100 mg/L (d)	Readily Biodeg
22	435	141-17-3	Adipic acid, bis[2-(2-butoxyethoxy)ethyl]ester										
24	399	33703-08-1	Adipic acid, diisononyl ester	>10 g/kg	90-Day Oral Diet NOAEL 500 mg/kg/day (rat) NOAEL 274 mg/kg/day (dog)	Negative (Ames, mouse lymphoma)				> 2.6 mg/L			Readily Biodeg. 73% in 28 days OECD 301F
26	427	27178-16-1	Adipic acid, diisodecyl ester	20.5 g/kg									Readily Biodeg. 68% in 28 days OECD 301F
32	511	16958-92-2	Adipic acid, ditridecyl ester	16 g/kg	90-Day Dermal (rat) Doses of 800 and 2000 mg/kg/d were well tolerated.	Negative (Ames)	Negative (micronucleus)	Dermal (rat) NOAEL = 800 mg/kg Sperm morphology, uterus+ epididymides weight-no effect		>5000 mg/L	4800 mg/L		Not Readily Biodeg 57% in 28 days OECD 301B
25	412	103-24-2	Azelaic acid, bis(2-ethylhexyl)ester	8.72 ml/kg						>1000 mg/L			Readily Biodeg. 81% in 28 days OECD 301B
29	469	28472-97-1	Azelaic acid, diisodecyl ester	>2 g/kg						>10,000 mg/L			Primary Biodeg
12	230	106-79-6	Sebacic acid, dimethyl ester										
26	469	122-62-3	Sebacic acid, bis(2-ethylhexyl) ester (e, e)	9.5 g/kg (mice) >12.8 g/kg (rat)	3-Week Oral Diet (rat) LOAEL 2% Diet (~1000 mg/kg/day) Liver weight increase and peroxisome proliferation reported 19-Week Orat diet (rat) NOAEL 200 ppm dict	Negative (Ames)		19-Week Oral Diet (Rat) NOAEL 200 ppm diet (~10 mg/kg/day) No adverse reprod effects		>1000 mg/L	>1000 mg/L	>1000 mg/L	Not Readily Biodeg. 65% in 28 days OECD 301B

Highlighted rows are not on the HPV list but included to facilitate category evaluation

(a) Toxicology data for dibuty maleate were reported in OECD SIDS dossier for Maleic acid, dibutyl ester (CAS 105-76-0). Also see IUCLID 1996 hedset

(b) LD50 value reported in Elder (1984). Final safety assessment of dioctyl adipate and diisopropyl adipate. Robust summary not prepared duc to limited or insufficient information.

(c) LD50 value or toxicity findings reported in secondary reference (Patty's Toxicology, Chapter 79: David et al. 2001). Robust summaries were not prepared due to limited or insufficient information.

(d) No mortality in these aquatic species was observed at water saturation levels of test material.

(e) Toxicology data for di(2-ethylhexyl) sebacate have been reported in BIBRA Toxicology Profile (1996).

Table 3C. Group C - Aliphatic Esters, comprised of Monoacids and Dihydroxy Alcohols - "Glycol Esters" Summary Table of Toxicology and Biodegradation Data

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Aber.)	Toxicity to Reproduction	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50	Daphnia LC50 or LL50	Algal LC50 or LL50	Biodegradation %
15	258	71839-38-8	Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol	>2 g/kg	28-Day Oral Gavage (rat) Doses up to 1000 mg/kg were well-tolerated.	Negative (Ames)	Negative (human peripheral lymphocytes) No chrom aber.						Readily Biodeg. 87.3% in 28 days OECD 301B
20	329	111-60-4	Stearic acid, 2-hydroxyethyl ester	> 5 g/kg									
20	375	7434-40-4	Triethylene glycol, diheptanoate (a)			Negative (Ames)				>30 mg/L (>1000 mg/L with emulsifier)	9.1 mg/L	559-712 mg/L	65% in 28 days OECD 301B
21	343	1323-39-3	Propylene glycol, monostearate (b)	25.8 g/kg	6-Month Oral Study at 10% in diet No signs of toxicity in rats, dogs	Negative (Ames)							
22	419	70729-68-9	Heptanoic acid, oxybis(2,1-ethanediyloxy-2,1-ethanediyl) ester	25 g/kg	28-Day Oral NOAEL 1000 mg/kg	Negative (Ames)	Negative (CHO)			720 mg/L	3800 mg/L	16 mg/L	Readily Biodeg. 98% in 28 days OECD 301E
23	368	67989-24-6	9-Octadecenoic acid (Z)-, ester with 2,2-dimethyl-1,3-propanediol (Monoester)	> 10 ml/kg							~ 2000 mg/L		Readily Biodeg. 73% in 28 days OECD 301B
24	431	68583-52-8	Decanoic acid, mixed diesters with octanoic acid and triethylene glycol										
24	447	18268-70-7	Hexanoic acid, 2-ethyl-, diester with tetraethylene glycol										
27	441	22788-19-8	Propylene glycol dilaurate (b)	> 34.6 g/kg (c)									
38	595	627-83-8	Stearic acid, ethylene ester (Diester)	> 16 g/kg									
39	605	105-62-4	Oleic acid, propylene ester (Diester)										
39	609	68958-54-3	Propylene glycol diisostearate (b)	> 25.8 g/kg (c)									
41	633	42222-50-4	9-Octadecenoic acid (Z)-, 2,2-dimethyl-1,3-propanediyl ester (Diester)										

Highlighted rows are not on the HPV list but included to facilitate category evaluation

Footnotes:

a) Data for triethylene glycol diheptanoate based on IUCLID toxicology database for CAS 734-40-4.

b) Data for various ethylene or propylene glycol esters and their diesters were obtained from several references including: W Johnson, Internat. J Toxicol. 18 (Suppl. 2): 35-52 (1999) RL Elder, J. Amer. Coll. Toxicol. 1(2): 1-12 (1982); RL Elder, J. Amer. Coll. Toxicol. 2(5): 101-124 (1983).

c) Read across for the oral LD50 for the propylene glycol dilaurate was based on the LD50 for propylene glycol monolaurate; the diester was considered to be similar or less toxic than the corresponding monoester. similarly, the oral LD50 for propylene glycol distearate was based on its monostearate.

Table 3D. Group D - Aliphatic Esters, comprised of Monocids and Sorbitan - "Sorbitan Esters" Summary Table of Toxicology and Biodegradation Data

Total Carbon Number in Ester	MW	CAS Number	Chemical Name	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Abs.)	Toxicity to Reproduction	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50	Daphnia LC50 or LL50	Algal LC50 or LL50	Biodegradation %
18	346	1338-39-2	Sorbitan, monolaurate	36 g/kg	13-wk Feeding Study (Rat) LOAEL ~2200 mg/kg (2.5% diet)					75 mg/L			Not Readily Biodeg. 60% in 28 days OECD 301D (BOD)
18-20	346-374	68154-36-9	Fatty acids, coco, monoesters with sorbitan (main fatty acids are lauric and myristic acids)										
24	431	1338-41-6	Sorbitan, monostearate	> 15.9 g/kg	6-wk Feeding Study (Rat) NOAEL 2500 mg/kg/d (5% diet) 80-wk Feeding Study (Mice) NOAEL 2600 mg/kg/day (2% diet) 2-Yr Feeding Study (Rat) NOAEL 5000 mg/kg/d (10% diet)	Negative (Ames)	Negative (Hamster embryo cells in vitro)	In 2-yr feeding study in rats, no effect seen on gestation and fertility at 5, 10 and 20% in the diet. Survival of newborn and maternal lactation diminished at 20% in diet.					
24	430	1338-43-8	Sorbitan, monooleate	> 39.8 g/kg	16-wk Feeding Study (Rat) LOAEL ~1800 mg/kg/d (2.5% diet) 2-year Feeding Study (Rat) NOAEL (5%diet)					> 1000 mg/L			Not Readily Biodeg. 62% in 28 days OECD 301D (BOD)
33	569	8007-43-0	Sorbitan, sesquioleate	> 39.8 g/kg									
38	668	228573-47-5	Sorbitan, fatty acids C6-10, tetraester	>2.0 g/kg	28-Day Oral NOAEL 1000 mg/kg (rat)	Negative (Ames)				>1000 mg/L	>1000 mg/L	>1000 mg/L	Not Readily Biodeg. 70% in 28 days OECD 301D (BOD)
60	958	26266-58-0	Sorbitan, trioleate	> 39.8 g/kg									

Highlighted rows are not on the HPV list but included to facilitate category evaluation

Table 3E. Group E - Aliphatic Esters, comprised of Monoacids amd Trihydroxy or Polyhydroxy Alcohols - "Polyol Esters" Summary Table of Toxicology and Biodegradation Data

Total Carbon Number in Ester	MW	CAS Number	Chemical Name (Type Ester; Acid)	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Aber.)	Toxicity to Reproduction	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50	Daphnia LC50 or LL50	Algal LC50 or LL50	Biodegradation %
31	513	68130-53-0	Decanoic acid, mixed esters with heptanoic acid, octanoic acid and trimethylolpropane (TMP Ester; C7, 8, 10 Acid)										
			Trimethylolpropane esters of heptanoic and octanoic acid (TMP Esters; C7,8 acids)	Oral LD50 > 2000 mg/kg (rat)	28-Day oral toxicity (rat) NOAEL 100 mg/kg/day	Negative (Ames)	Negative Chrom. Aber.			>1000 mg/L	>1000 ppm	>1000 ppm	Not Readily Biodeg.
		71839-38-8	Heptanoic acid, ester with 2,2,4-trimethyl-1,3-pentanediol (TMP Esters; C7 acids)	Oral LD50 > 2000 mg/kg (rat)	28-Day oral toxicity (rat) well tolerated 1000 mg/kg/day	Negative (Ames)	Negative Chrom. Aber.			>1020 mg/L			Not Readily Biodeg.
		180788-27-6	Hexanedioic acid, mixed esters with C10-rich, C9-11 isoalcohols and TMP (TMP+other alcohols Mixed Esters, C6 dioic acids)	Oral LD50 > 2000 mg/kg (rat)	28-Day oral toxicity (rat) well tolerated 1000 mg/kg/day	Negative (Ames)	Negative Chrom. Aber.			>1000 mg/L	>1000 mg/L	>1000 mg/L	Not Readily Biodeg.
24	415	11138-60-6	Decanoic acid, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol octanoate (TMP Ester; C8, C10 Acid)	Oral LD50 > 5000 mg/kg (rat)	28-day Dermal (rat) NOAEL 2000 mg/kg/day	Negative (Ames)	Negative Chrom. Aber.	unpublished data will obtain copy of final report	unpublished data will obtain copy of final report	>1035 mg/L	>2570 ppm	>1018 ppm	Not Readily Biodeg.
33	555	126-57-8	Nonanoic acid, triester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP Triester; C9 Acid)	Dermal LD50 2000 mg/kg			Negative Cytogenetic			>1000 mg/L	>9.3 mg/L	>4.4 mg/L	Not Readily Biodeg.
56	875	68002-79-9	Fatty acids, C14-18 and C16-18 unsatd, triesters with trimethylolpropane (TMP Triester; C14-18 satd, C16-18 unsatd Acid)										
24	417	70024-57-6	9-Octadecenoic acid (Z)-, ester with 2-ethyl-2-(hydroxymethyl)-1,3-propanediol (TMP Monoester, Oleic C18 Acid)	Dermal LD50 > 10 ml/kg						2.027 mg/L			Readily Biodeg.
60	928	57675-44-2	9-Octadecenoic acid (Z)-, 2-ethyl-2-[(1-oxo-9-octadecenyl)oxy]methyl]-1,3-propanediyl ester, (Z)- (TMP Diester; Oleic C18 Acid)										Not Readily Biodeg.
33	529	67762-53-2	Carboxylic acids, C5-9, tetraesters with pentaerythritol (PE Tetraester; C5-9 Acids)	Oral LD50 > 1940 mg/kg (rat)		Negative (Ames)				>5012 mg/L			Not Readily Biodeg.
37	641	68130-51-8	Decanoic acid, mixed esters with heptanoic acid, isovaleric acid, octanoic acid and pentaerythritol (PE Mixed Ester; C7, 8 Acids)										
	613	68424-31-7	Fatty acids, C5-10, esters with pentaerythritol (PE Ester; C5-10 Acids)									>4.4 mg/L	
		68130-55-2	Hexanedioic acid mixed esters with decanoic acid, heptanoic acid, octanoic acid and PE (PE Mixed Esters; C6,7,8,10 acids)	Oral LD50 > 2000 mg/kg (rat)	28-Day dermal toxicity (rat) NOAEL 500 mg/kg/day	Negative (Ames)	Negative Chrom. Aber.			>5076 ppm	>5076 ppm	<324 ppm	Not Readily Biodeg.
41	697	14450-05-6	Nonanoic acid, neopentanetetrayl ester (PE Tetraester; C9 Acid)										
77	1202	115-83-3	Pentaerythritol, tetrastearate (PE Tetraester; C18 Acid)										

Total Carbon Number in Ester	MW	CAS Number	Chemical Name (Type Ester; Acid)	Acute Oral LD50	Repeated Dose Toxicity	Genetic Tox (Point/Gene Mutation)	Genetic Tox (Chrom. Aber.)	Toxicity to Reproduction	Developmental Toxicity/ Teratogenicity	Acute Fish LC50 or LL50	Daphnia LC50 or LL50	Algal LC50 or LL50	Biodegradation %
			Fatty acids, C5-9, esters with pentaerythritol (PE Esters; C5-9 acids)	Oral LD50 > 2000 mg/kg (rat)		Negative (Ames)							
	1100		Fatty acid, C6-10, tetraesters with PE (PE Tetraesters; C6-10 Acids)	Oral LD50 > 2000 mg/kg (rat)	28-Day oral toxicity (rat) NOAEL 1000 mg/kg/day	Negative (Ames)	Negative Chrom. Aber.			>5000 mg/L	>5000 mg/L	>5000 ppm	Not Readily Biodeg.
77	1188	68648-28-2	Linseed oil, ester with pentaerythritol (PE Ester: oleic, linoleic, linolenic C18 acids)	Oral LD50 > 5000 mg/kg (rat)									
77	1190	68334-18-9	Fatty acids, tall oil, tetra esters with pentaerythritol (PE Tetraester; oleic and linoleic C18 acids)										
60	927	70983-72-1	Fatty acids, C5-10, esters with dipentaerythritol (DiPE hexaester; C5-10 Acids)	Oral LD50 > 5000 mg/kg (rat)								>4.4 mg/L	
60	955	67762-52-1	Carboxylic acids, C5-9, hexaesters with dipentaerythritol (DiPE hexaesters; C5-C9 Acids)	Oral LD50 > 1940 mg/kg (rat)		Negative (Ames)				>5012 mg/L			Not Readily Biodeg.
			Fatty acids, C5-9, esters with dipentaerythritol (DiPE Ester; C5-9 acids)	Oral LD50 > 2000 mg/kg (rat)		Negative (Ames)							

Highlighted rows are not on the HPV list but included to facilitate category evaluation

Appendices

Robust Summaries

With reference to the SIDS Data Matrix the reports have been evaluated and assessed according to the Klimisch criteria as described in previous sections.

1 = Reliable without restrictions,
2 = Reliable with restrictions,
3 = Not reliable,
4 = Not adequate.

This chapter will focus on each study specifically. The order of presentation will be physico-chemical data, environmental fate data, ecotoxicity and toxicity. EPIWIN data were not included in the summary tables. The following references were not included in the summaries. Results from these references were incorporated directly into the SIDS data matrix.

1	SIDS Initial Assessment Report for 10'" SIAM	2000
2	HPV SIDS dossier for 7,9 Adipates	**2000**

List of Abbreviations

a	Absolute to body weight
	Absent
+	Present
a.i.	Active ingredient
B P	Boiling point
d	Decrease
dc	Decrease (significant)
DR	Dose related
F	Female
Hb	Haemoglobin
I	Increase
ic	Increase (significant)
M	Male
N/A	Not applicable
r	Relative to body weight
$THCO_2$	Theoretical amount of CO2
TC02	Theoretical amount of CO_2
TS	Test substance
V P	Vapour pressure
w s	Water solubility

Robust Summaries were prepared by Manon Beekhuizen, Mieke van der Bruggen, Ineke Gubbels, Peter Jan Slangen, Marleen Teunissen, An Vanwormhoudt and Wendy van de Wiel.

Appendix 1 - Physico-Chemical Data for the Aliphatic Esters

GROUP A

No data available.

GROUP B

1.07

Title	Determination of partition coefficient
Date of report	March 30, 1994.
GLP	No.
Test substance	CAS: 122-62-3; purity not indicated.
Test method	92/69/EEC.
Procedure	The shake-flask method (method A.8 of Commission Directive) was used.
Results	P_{ow} 5.55 x 1 0^3 at 21±0.5°C.
Conclusion	log Pow 3.74
Rev. note	The above mentioned was the only information available.
Klimisch criterium	4 Limited information

GROUP C

1.08

Title	Thermodynamics of organic chemical partition in soils. 1. Development of a general partition model and application to linear isotherms (from: Environ. Sci. Technol.)
Date of report	1994.
GLP	No.
Test substance	CAS: 627-83-8 and 123-95-5, ethylstearate and n-butylstearate, purity not indicated.
Guidelines	Not indicated.
Procedure	A general thermodynamic partition model for organic carbon-based linear and non-linear sorption from solution was formulated. By using appropriate concentration units in the solution and sorbed phases, the conventional Freundlich partition coefficient was found to be related to the aqueous-phase activity coefficient and sorbate solubility in the humic phase. The model could calculate molar volume, activity coefficients, solubilities and Flory interaction parameters for stearate ester/PVC systems.
Rev. note	No SIDS-endpoint.
Klimisch criterium	4 No SIDS-endpoint.

1.09

Title Solubility of plasticizers for XXXX sheeting.

Date of report January 26, 1982.

GLP No.

Test substance CAS 70729-68-9, purity not indicated

Guideline Not specified.

Test System Flask Method (modified).

Test substance (30 mL) was shaken with 150 mL water for 30 minutes. After centrifuging (11,000 rpm) the aqueous layer was held overnight in a separatory funnel at 20 °C. 100 mL of the aqueous phase was extracted five times with 50 mL Freon®1 13 solvent and dried with anhydrous sodium sulphate for 2h. The extracted was concentrated, dried and weighed.

Results

Weight % test substance in water at 20 °C	
	CODE28
Flask 1	0.126
Flask 2	0.118
A verage	0.122

Conclusion The solubility in water of CODE28 is 1.22 g/L

Rev. note

1. Shaking of the test substance was performed for only 30 minutes at unspecified temperature. Only two flasks were included with identical shaking intervals. Equilibration was only performed overnight. It cannot be excluded that saturation had not yet been reached after 30 minutes at the applied temperature nor that the solution was not equilibrated after one night. Furthermore, the shaking temperature may have been too high causing degradation of the test substance.
2. Solubility was calculated on basis of the weight of the residue. As no analysis of the residue was performed, it cannot be excluded that impurities were included. Furthermore, the extraction method was not validated.
3. Minor remark: pH of the solutions was not determined.

Klimisch Criterium 3 Solution may have been over- or under-saturated (note 1); Impurities may have been included (note 2)

1.10

Title Octanol/water partition coefficient and lipid solubility of CODE28 plasticizer,

Date of report December 4, 1981.

GLP No.

Test substance CAS 70729-68-9, CODE28 (purity 88% in mixed esters)

Test method OECD 107 (1981)

Procedure Octanol and water were mutually saturated with each other. Test substance (20.0 mg in 5 mL octanol) was mixed with octanol (total volume 5, 7 and 10 mL in flask A, B and C, resp.) and water (40, 38 and 35 mL in flask A, B and C, resp.) in duplicate vessels at 25°C. The mixtures were shaken for 15 min., centrifuged and re-equilibrated to 25°C for 24h. Concentrations were determined using a gas chromatograph.

Results

Treatment	*A1*	*A2*	*B1*	*B2*	*C1*	c2
TS (mg)	20	20	20	20	20	20
Volume of octanol [mL]	5	5	7	7	10	10
Volume of water [mL]	40	40	38	38	35	35
Concentration in octanol phase [mg/L]	3880	3940	2885	2875	1990	2020
Concentration in aqueous phase [mg/L]	5.57	4.97	3.69	3.44	3.77	2.77
Recovery [%]	98	100	1102	101	100	101
Pow	7.0'10'	$7.9*10^2$	$7.8*10^2$	$8.4*10^2$	$5.3*10^2$	$7.3*10^2$
Average Pow±RSD	$7.4*10^2$±9.5%		$8.1*10^2$±4.9%		$6.3*10^2$±22%	
Average Pow±SD	$7.3*10^2$±$1.1*10^2$					
10log(Pow)	2.86					

Conclusion	log P_{ow} 2.86 at 25°C
Rev. note	1. Minor remarks: Volume ratios of the 3 runs were very similar, but this will not influence the study. pH of the aqueous phases were not determined.
Klimisch criterium	1

GROUP D

No data available.

GROUP E

1.11

Title	Schedule II notification related studies for **CAS: 126-57-8; 3.** Melting (Pour) point.
Date of report	July 24, 1997.
GLP	No.
Test substance	CAS: 126-57-8; trimethylolpropane tripelargonate, purity 100%.
Test method	OECD 102.
Procedure	~4 mL (~4 g) **CAS:** 126-57-8 was placed in a 15 mL glass test tube. The tube was cooled in liquid nitrogen. The tube with frozen content was removed and allowed to warm in the air. Every 15 seconds the temperature was measured in the **CAS: 126-**57-8 (8 mm from bottom, centre). The test (cooling, warming) was repeated three times, now with the sample in horizontal position during warming to allow observation of substance flow.
Results	The apparatus was calibrated with tap water. The pour temperature of water was -4°C according to the test. Results for **CAS:** 126-57-8: see table below.

Observed pour points of CAS: 126-57-8 [°C]			Mean pour point [°C]
-53	-62	-68	-61

Conclusion	Pour point **CAS: 126-57-8**: -61±8°C.
Rev. note	1. The method used in the test was probably not accurate. The only information available about the accuracy was a validation of the system with tap water. The measured pour temperature was -4°C. The low value (-4°C instead of 0°C) could be partly due to impurities in the tap water, but is probably also related to the accuracy of the method. The study reliability is lowered. 2. Although it was stated that all laboratory work undertaken was done using Good Laboratory Procedures, no signed GLP statement was included in the report.
Klimisch criterium	**2** Accuracy method.

1.12

Title	Schedule II notification related studies for **CAS: 126-57-8;** 4. Partition coefficient; P_{ow}
Date of report	July 24, 1997.
GLP	No.
Test substance	CAS: 126-57-8; trimethylolpropane tripelargonate, purity 100%.
Test method	Based on OECD 105.
Procedure	Based on water solubility results, it was assumed that the concentration of **CAS: 126-**57-8 in the aqueous phase of a P_{ow} experiment could not be determined with acceptable accuracy. The P_{ow} test was not performed and P_{ow} was estimated based on the solubilities of **CAS:** 126-57-8 in octanol and water. n-Octanol and **CAS: 126-57-8** (0.1-l 0 g/mL) were placed in six 4 mL glass vials and mixed for ~1 hour at 23°C.

Results For all concentrations homogeneous (single phase) solutions were formed.
Conclusion Solubility in n-octanol and water were respectively >900 g/L and 8.4 mg/L (note 1). Log P_{ow} >2.8 at 23±1°C.
Rev. note
1. Determination of solubility of **CAS: 126-57-8** in n-octanol was based on visual (subjective) evaluation. No analyses were performed.
2. This test can be used for the estimation of the log(P_{ow}) of **CAS: 126-57-8.** However, only the solubility of **CAS: 126-57-8** in n-octanol was determined in this test. The water solubility was taken from another study. The partition of a mixture of water and n-octanol may be estimated by using the separate solubilities. It is clear from this report that most of the test substance will be found in the octanol-phase.
3. Although it was stated that all laboratory work undertaken was done using Good Laboratory Procedures, no signed GLP statement was included in the report.

Klimisch criterium 2 Accuracy method (note 1 and 2).

1.13
Title Test substance: **CAS: 11138-60-6** Physical/chemical testing for CEPA regulations; 4. Boiling point/range
Date of report August 30, 1996.
GLP No.
Test substance CAS: 11138-60-6; multicomponent mixture.
Test method OECD 103.
Procedure The test substance (10 mm) was put above an air layer (2 mm) in a sealed glass Pasteur pipette and placed in a forced air oven at 305°C and 102 kPa.
Results Movement of test substance was <5 mm, no colour change.
Conclusion Boiling point >300°C at 102 kPa.
Rev. note A modified method of Siwoloboff was used in this test. This method seems less accurate than the original one.
Klimisch criterium 2 Accuracy method.

1.14
Title Test substance: **CAS: 11138-60-6** Physical/chemical testing for CEPA regulations; 8. Partition coefficient; K_{ow}
Date of report August 30, 1996.
GLP No.
Test substance CAS: 11138-60-6; multicomponent mixture.
Test method OECD 107.
Procedure Mutually saturated n-octanol and ultrapure water were used in the test. The test was performed with 12 mL water and 6, 12 and 24 mL n-octanol; 300 µL of a solution of **CAS: 11138-60-6** in acetonitrile (2.54 g/L) was added. A blank with 12 mL water and 12 mL n-octanol was included. After 21 min. of shaking (22°C), the solutions were centrifuged, the phases separated and analysed by GC-FID. In the water layer filtration and extraction with methyl t-butylether (2 mL) preceded the analyses with GC-FID.
Results **CAS: 11138-60-6** was not found in any of the aqueous phases, indicating that its concentration was less than the limit of detection of 0.3 µg/mL.

Amount solution (mL)		Concentration CAS: 11138-60-6 (µg/mL)			
Water	Octanol	aq. phase	octanol phase	K_{ow}	log(K_{ow})
12	12	<0.3	64	>213	>2.3
12	6	<0.3	139	>462	>2.7
12	24	<0.3	28	>92	>2.0

Conclusion log(K_{ow}) >2.7 at 22%.
Rev. note K_{ow} values are minima, as concentrations of **CAS: 11138-60-6** in the aqueous phases were less than the detection limit.
Klimisch criterium 1

1.15

Title Test substance: **CAS: 11138-60-6** Physical/chemical testing for CEPA regulations; 10. Solubility in water

Date of report August 30, 1996.

GLP No.

Test substance CAS: 11138-60-6; multicomponent mixture.

Test method OECD 105

Procedure The flask method was used. The solubility was determined in ultrapure water. 4 mL (-3.8 g) **CAS: 11138-60-6** was added to 47 mL of solvent in a 50 mL vial (duplicate samples). The vials were shaken at 22±1 °C for 2.1 and 4.8 days. Following centrifugation, the water samples were sampled with a syringe, extracted with 2 mL of methyl t-butylether and the organic extracts were analysed by GC-FID.

Results Concentration **CAS: 11138-60-6** in test solutions after 2.1 and 4.8 days was respectively 0.44 and 0.51 mg/L

Conclusion Water solubility **CAS: 11138-60-6:** 0.48±0.14 mg/L at 22±1 °C.

Rev. note

1. CAS: 11138-60-6 was not a pure substance, although guideline addresses essentially pure substances.
2. The pH during the test was not reported. Since esters can be hydrolysed in water and pH is an important factor in this, it is an important deficiency of the report. It was stated that visually no difference in volume of oil at the water surface was observed. This is not adequate.
3. It was stated that a statement of GLP compliance for this study was included in the APPENDIX. However the report that was received contained no APPENDIX.
4. The Method Detection Limit (statistical estimate of the minimum concentration of **CAS: 11138-60-6** in water that could be detected with 90% confidence) was 0.5 µg/mL. The result of the report is rather close to this value.

Klimisch criterium 3 Purity test substance not reported (note I), stability test substance questionable (note 2), result close to detection limit (note 4).

1.16

Title Test substance: **CAS: 11138-60-6** Physical/chemical testing for CEPA regulations; 12. Vapour pressure

Date of report August 30, 1996.

GLP No.

Test substance CAS: 11138-60-6; multicomponent mixture.

Test method OECD 104.

Procedure The isoteniscope method described in OECD 104 was used.

Results LOD: 13 Pa.

Temperature [°C]	**20**	**25**	**50**	100	150	200	250	300	350	**375**
Vapour pressure [Pa]	<13	<13	<13	**40**	**267**	**1107**	**3466**	**8666**	21998	58662

Conclusion Vaoour pressure at 25°C: <1 3 Pa.

Rev. note The recommended range of vapour pressures using this method is 10^2-1 0^5 Pa according to OECD 104. The vapour pressure of **CAS: 11138-60-6** at temperatures below 150°C lies below this level. At 350°C decomposition of **CAS: 11138-60-6** was observed. So part of the increase in vapour pressure at temperatures 350 and 375°C could be due to other compounds formed in this decomposition.
In the report is stated that above 670 Pa, the repeatability is -10%. Below this level no information is available in the report. Since OECD 104 recommends this method for vapour pressures in the range 1 0^2-10^5 Pa also the value at 150°C is acceptable. Including also the decomposition of the test substance it can be concluded that in this test only values of vapour pressures between 150 and 300°C are reliable.

Klimisch criterium 2 Value at 25°C less reliable.

1.17

Title	Calculation of log P for **CAS: 11138-60-6.**
Date of report	November 26, 1996.
GLP	Yes.
Test substance	CAS: 11138-60-6 (100% trimethylolpropane caprylate caprate)
Test method	CLOGP Windows (Version 1 .0); fragment addition methodology.
Test system	**Procedure** The computer software program CLOGP estimates the log P value from the structure of the compound. As **CAS: 11138-60-6** is likely to be a mixture of isomers, three chemical structures were chosen or considered in calculating the log P: 1. The isomer in which the acid groups were straight-chain (i.e. no branching). 2. The isomer which had one branch in each of the acid groups (i.e. methyl branch at the penultimate or next to the last carbon). 3. The isomer which had two or more points of branching in the acid groups. The chemical structure drawing program "ChemDraw Pro" for Windows was used to draw the chemical structure and to get the SMILES notation of the three structural isomers. The latter was entered separately in CLOGP Windows and the log P values were calculated. Reference chemicals were used to check on how well the CLOGP program agrees with log P values reported by A.J. Leo, 1993.
Results	For the **CAS: 11138-60-6** isomer in which the acid groups were straight-chain, the log P value was 12.1. For the isomer which had one branch in each of the acid groups, the log P value was 11.7. For the isomer which had two or more points of branching in the acid groups, the log P value was 11 .1. Most calculated log P values of the reference chemicals agreed well with log P values reported by A.J. Leo, 1993.
Conclusion	log P values range from 11 .1 to 12.1, depending on the degree of branching or non-branching of the acid groups in the isomers.
Rev. note	The software program gives an estimation of the log P values and so they should be carefully evaluated. As the values are so unrealistically high, they might not be very useful.
Klimisch Criterium	2

1.18

Title	Flashpoint, flammability and reactivity determination for **CAS: 11138-60-6**
Date of report	October 7, 1996.
GLP	Yes.
Test substance	CAS: 11138-60-6; purity not indicated.
Test method	ASTM method D 93, US EPA SW-846 volume II, part 7.3.
Procedure	The flashpoint was measured using a Pensky-Marten closed cup tester. Reactivity of **CAS: 11138-60-6** was determined by the measurement of hydrogen cyanide and hydrogen sulphide evolved in a test according to EPA.
Results	**CAS: 11138-60-6** did not flash within 24-77°C; No measurable quantities of hydrogen cyanide and hydrogen sulphide were released during the reactivity test.
Conclusion	**CAS:** 11138-60-6 is not flammable and released HCN and H_2S were respectively <0.1 and <0.5 mg/kg.
Rev. note	Since no SIDS-endpoints were available in the report, only a minor summary of the tests is included above.
Klimisch criterium	4 No SKIS-endpoints.

1.19

Title Schedule II notification related studies for **CAS:** 126-57-8; 6. Boiling point

Date of report May 25, 1997.

GLP Yes.

Test substance CAS: 126-57-8; trimethylolpropane tripelargonate, purity 100%.

Test method OECD 103.

Procedure The test substance (40 mm) was put in a sealed glass Pasteur pipette and inserted into the injection port of a gas chromatograph (T_{max} 314±5°C) at 102±1 kPa.

Results No condensation of a significant amount of test substance (T<314°C) and no significant bubbles were formed (314°C).

Conclusion Boiling point >300°C at 102±1 kPa.

Rev. note
1. A modified method of Siwoloboff was used in this test. This method seems less accurate than the original one.
2. GLP statement is signed by the study director. Although an external GLP auditor was mentioned, this person did not sign the GLP statement.

Klimisch criterium 2 Accuracy method (note 1)

1.20

Title Schedule II notification related studies for **CAS:** 126-57-8; 8. Solubility in water

Date of report May 25, 1997.

GLP Yes.

Test substance CAS: 126-57-8; trimethylolpropane tripelargonate, purity 100%.

Test method OECD 105.

Procedure The solubility in water was determined using the flask method. 4 mL (~4 g) test substance was added to 45 mL ultrapure water in a 50 mL test tube. The test tubes were mixed on a rotary mixer (5 rpm) at 22-23°C [note 1] for 24, 70 and 139 hours. Following centrifugation and equilibration to room temperature (1 hour), TOC analysis (total carbon and total inorganic carbon content were determined from calibration curves) was performed for water samples. A blank sample (ultrapure water) was also run for 139 h.

Results See table below.

Mixing time [h]	TOC in water [mg/L]	CAS: 126-57-8 in water [mg/L][1]	RSD [%]
24	6.5	9.1	2
70	6.0	8.5	2
139	6.0	8.4	1

[1] TOC is assumed to be composed of only **CAS:** 126-57-6 [note 2].

Conclusion Water solubility **CAS:** 126-57-8: 8.4±0.1 mg/L at 23°C.

Rev. note
1. Nothing was said about temperature control during the test; only air temperature was reported. Temperature is an important factor in the water solubility of the test substance. There is no clear view of the temperature range during the study.
2. The pH during the test was not reported. Since esters can be hydrolysed in water and pH is an important factor in this, it is an important deficiency of the report. Further only TOC analysis was performed, so it cannot be excluded that the measured concentration consisted partly of hydrolysates of **CAS: 126-57-8.**
3. GLP statement is signed by the study director. Although an external GLP auditor was mentioned, this person did not sign the GLP statement.
4. It was suggested, based on results for a solubility standard, that the observed solubility of **CAS: 126-57-8** was due to the dissolution of a relatively minor (<2%) component of **CAS: 126-57-8,** which was relatively more water soluble than the majority of **CAS: 126-57-8.** As the guideline is intended for pure compounds, the method may not be applicable to **CAS:** 126-57-8.

Klimisch criterium 3 Temperature control (note I), stability test substance (note 2), composition **CAS: 126-57-8** (note 4).

1.21

Title	Schedule II notification related studies for **CAS: 126-57-8;** 10. Vapour pressure
Date of report	May 25, 1997.
GLP	No.
Test substance	CAS: 126-57-8; trimethylolpropane tripelargonate, purity 100%.
Test method	ASTM D2879-92, OECD 104.
Procedure	The isoteniscope method described in OECD 104 was used.
Results	LOD: 13 Pa.

Temperature [°C]	**25**	**30**	**40**	**50**
Vapour pressure [Pa]	**21**	**27**	**40**	**57**

Conclusion	Vapour pressure at 25°C: 21 Pa.
Rev. note	1. The recommended range of vapour pressures using this method was 10^2-1 0^5 Pa. The vapour pressure of **CAS:** 126-57-8 lies below this level. The repeatability of the test is not obvious. In OECD 104 is stated that the repeatability in the recommended range is 5-l 0%. For other ranges no information is available. Since all vapour pressures measured in this test were <100 Pa, the study reliability is lowered. 2. GLP statement is signed by the study director. Although an external GLP auditor was mentioned, this person did not sign the GLP statement. The GLP statement indicates that physical/chemical testing was conducted in accordance with OECD guidelines for GLP. However, this work was subcontracted to a laboratory that was not accredited as a facility that complies with GLP.
Klimisch criterium	2 Repeatability study not clear (note 1).

Appendix 2 - Environmental Fate Data and Pathways for the Aliphatic Esters

GROUP A

No data available.

GROUP B

2.01

Title	Biodegradation Studies of **CAS: 16958-92-2** (Closed bottle test)
Date of report	October 13, 1986.
GLP	No.
Test substance	CAS: 16958-92-2; purity not indicated.
Test method	OECD 301D (1981).
Test system	**CAS: 16958-92-2** was dissolved in the carrier 2,2,4,4,6,8,8-heptamethylnonane (HMN) (30 mg/ml). In the 1st experiment the test solution was added directly to the BOD bottle. In the 2nd experiment an emulsified test solution was added. Inoculum was obtained from a waste treatment facility. A few controls were run with each experiment: - BOD medium + inoculum + test compound; - BOD medium (without inoculum or test compound); - BOD medium + inoculum; - BOD medium + inoculum + HMN (0.1 ml); - BOD medium + inoculum + naphthalene (2 mg C/l); All test compounds and controls were prepared in sets of 6 replicates; the oxygen consumption was measured after 5, 15 and 28 days for 2 from each set. The bottles were incubated for 28 days. Readings were performed with the Winkler dissolved oxygen method. Determination of COD **of CAS: 16958-92-2** (in duplicate) was performed at three concentrations. The percentage biodegradation of **CAS: 16958-92-2** was based on COD and BOD values.
Results	COD: 2.5 mg O_2/mg **CAS: 16958-92-2.** After 5/15/28 days incubation, values for degradation of (based on BOD and COD values): - **CAS: 16958-92-2:** 1.3, 6.8 and 16% (not emulsified samples, 1st exp.); - Positive control (naphthalene): 52, 61 and 69% (not emulsified samples, 1st exp.); - **CAS: 16958-92-2:** 4.8, 19 and >23% (emulsified samples, 2nd exp.); - Positive control (naphthalene): 54, 54 and 95% (emulsified samples, 2nd exp.);. No degradation of HMN was apparent. Higher rates of biodegradation in emulsified samples are probably due to the increased surface area on which micro-organisms can obtain growth substrate.
Conclusion	Not readily biodegradable.
Rev. note	1. It is doubtful whether the positive control met the validity criteria for ready biodegradability (260% biodegradability within 14 days). If the positive control did not meet this criteria, this study is observed as less reliable, and in this case the test should be repeated. 2. An insufficient number of CO_2 samples was taken. According to the guideline samples should be taken every second or third day during the first ten days and every fifth day until the 28th day. 3. Conclusion drawn in the test report concerning "It is likely that . . . **CAS: 16958-92-2** will be rapidly biodegradaded" is contrary to the OECD criteria of classifying a compound as 'readily biodegradable'. 4. Overestimation biodegradation when using COD value. 5. *Minor* remark: Temperature of incubation was not specified.
Klimisch criterium	*2*

2.02

Title	Determination of the primary biodegradability of **CAS: 16958-92-2** by the co-ordinating European Council's CEC L-33-A-93 test
Date of report	**28** July 1997.
GLP	No.
Test substance	CAS 16958-92-2 (purity not indicated)
Test method	CEC L-33-A-93 (Biodegradability of two-stroke cycle outboard engine oils in water)
Test system	**Treatments** For the test material: 1. six flasks with 150 ml CEC test medium + test/solvent solution (50 mg/l end concentration) + 1 ml inoculum. 2. two poisoned flasks with 150 ml CEC test medium + test/solvent solution (50 mg/l end concentration) + 1 ml of 0.03M $HgCl_2$. For the reference material: 1. six flasks with 150 ml CEC test medium + reference/solvent solution (50 mg/l end concentration) + 1 ml inoculum. 2. two poisoned flasks with 150 ml CEC test medium + reference/solvent solution (50 mg/l) + 1 ml of 0.03M $HgCl_2$. Additionally, two neutral flasks with 150 ml CEC test medium + 1 ml inoculum. Flasks with the reference material (CEC RL 130) were used as positive control. Abiotic degradation was determined in the poisoned flasks. The inoculum came from sewage collected at a municipal wastewater treatment plant. **Procedure** Extraction with 1 ,1,2-trichlorotrifluoroethane was performed on day 0 for the neutral flasks, 3 of the test and 3 of the reference flasks. The remaining flasks were incubated in a rotary incubator in the dark, at 26-27°C over a period of 21 days with continuous agitating (150 rpm). The primary biodegradation of the test and reference material was determined by quantitating the amount of unchanged material remaining in the flasks (2 poisoned flasks, 3 test and 3 reference flasks). This was done by infrared spectroscopy after extraction under acidic conditions. The absorbance of the C-H stretch at 2930 ± 10 cm^{-1} (CH_2-CH_3 absorbance band) was measured. Primary degradability was expressed as the percent difference in residual oil contents between the poisoned flasks and the respective test flasks.
Results	After 21 days of incubation, there was a primary biodegradation of 99% of the test substance and 96% of the reference standard.
Conclusion	Good primary biodegradability (99%).
Rev. note	1. Primary degradation is defined as the alteration in the chemical structure of a substance, brought about by biological action, resulting in the loss of a specific property of that substance. As only the absorbance of the C-H stretch (CH_2-CH_3 band) is documented, other degradation-paths are not included. 2. The results represent primary biodegradation and should not be interpreted to reflect ready biodegradation. As such, the study is not considered useful, but can be seen as supporting data.
Klimisch Criterium	3 Primary biodegradation (notes 1 and 2)

2.03

Title Aerobic Aquatic Biodegradation Studies of the Synthetic Esters: **CAS: xx, CAS: 16958-92-2** and **CAS: yy**

Date of report 22 January 1990.

GLP No.

Test substance CAS: 16958-92-2; purity not indicated.

Test method EPA 44(53): A.451 (1979) with some modifications.

Test system

Treatment -
- Inoculum: from activated sludge treatment at a Wastewater Treatment Plant. Amount inoculum: not specified.
- 2 flasks Treated (medium + inoculum + **CAS: 16958-92-2** (10 mg C/l));
- 2 flasks Positive Control (medium + inoculum + Rapeseed oil (10 mg C/l));
- 2 flasks Blank Control (medium + inoculum).

Procedure Incubation was performed under continuous shaking (150 rpm) in 2L flasks. Inoculum and medium were treated and aerated for 28 days at 25±3 °C. The outcoming air was passed through one CO_2-trap containing 10 ml 0.2N KOH. Flask traps were sampled at l-7 day intervals, depending on microbial activity. The amount of CO_2 was determined in the traps by backtitration with 0.2N I-ICI, after addition of $Ba(Cl)_2$ and phenolphthalein indicator. One day prior to the final sampling (day 27), the medium was acidified with 1 ml concentrated sulphuric acid.

Results **Table** below Biodegradation values for **CAS: 16958-92-2** and positive control. Values are corrected for blank control values.

	Mean % biodegradation [% of $ThCO_2$] on day:							
Treatment	**0**	**2**	**5**	**8**	**12**	**16**	**21**	**28**
CAS: 16958-92-2	**0.0**	**3.9**	11	**25**	**34**	**39**	**48**	**60**
Positive control	0.0	21	**46**	**58**	**65**	**69**	**72**	**74**

CAS: xx and CAS: yy are no HPV chemicals and are therefore not included in the test results.

Conclusion Not readily biodegradable.

Rev. note

1. According to OECD guidelines the main criteria for ready biodegradability is the 1 O-day window. This test report refers to another criterion for ready biodegradability: >60% conversion to CO_2 in 28 days. This is not in accordance with the OECD guidelines. However, the conclusion of this summary is based on the OECD ready biodegradability criteria. Furthermore not enough CO_2 samples were taken. According to the guideline samples should be taken every second or third day during the first ten days and every fifth day until the 28th day. As a result of this conclusions out of these data are not accurate.
2. An unofficial positive control was used; however it did meet the validity criterion (260% degradation within 14 days).
3. Test was not performed in darkness, which can influence the results due to possible photodegradation of the test substance.
4. For CO:! determination two or three absorber traps are normally used containing 100 ml base. In this test one absorber trap was used containing only 10 ml base, by which no ensurance can be given that all evolving CO_2 has been trapped. An overflow cannot be measured, but also cannot be excluded.
5. Test report did not specify that CO_2-free air was run through the test vessels during the test.

Klimisch criterium 3

2.04

Title	CEC test for determination of biodegradability of **CAS: 16958-92-2.**	
Date of repot-l	23 November 1992.	
GLP	No.	
Test substance	CAS: 16958-92-2 (purity not indicated)	
Test method	CEC L-33-T-82 (Biodegradability of two-stroke cycle outboard engine oils in water).	
Test system	**Treatments**	For the test material: 1. six flasks with 150 ml CEC test medium + test/solvent solution (50 mg/l end concentration) + 1 ml inoculum 2. two poisoned flasks with 150 ml CEC test medium + test/solvent solution (50 mg/l end concentration) + 1 ml of $HgCl_2$ (10g/l solution). For the reference material: 1. six flasks with 150 ml CEC test medium + reference/solvent solution (50 mg/l end concentration) + 1 ml inoculum 2. two poisoned flasks with 150 ml CEC test medium + reference/solvent solution (50 mg/l end concentration) + 1 ml of $HgCl_2$ (1 0g/l solution). Additionally, two neutral flasks with 150 ml CEC test medium + 1 ml inoculum. Flasks with the reference material (**CAS: zz**) were used as positive control. Abiotic degradation was determined in the poisoned flasks. The supernatant of sewage collected at a municipal wastewater treatment plant was used as inoculum.
	Procedure	Extraction with Freon 113 under acidic conditions was performed on day 0 for the neutral flasks, 3 of the test and 3 of the reference flasks. The remaining flasks were incubated in a rotary incubator in the dark, at 25±3°C over a period of 21 days with continuous agitating (100-200 rpm). The primary biodegradation of the test and reference material was determined by quantitating the amount of unchanged material remaining in the flasks (2 poisoned flasks, 3 test and 3 reference flasks) after 21 days. This was done by Fourier Transform Infrared Spectroscopy of the extracted test and reference solutions. The absorbance of the C-H stretch at 2930 cm^{-1} (CH_2-CH_3 absorbance band) was measured. Primary degradability was expressed as the percent difference in residual oil contents between the poisoned flasks and the respective test flasks.
Results	After 21 days of incubation, there was a primary biodegradation of more than 95% of the test substance and 56% of the reference standard.	
Conclusion	Good primary biodegradability (> 95%).	
Rev. note	1. No count was done of the colonies in the inoculum. The bacteria level of the inoculum should be $\geq 10^6$ CFU/ml according to the guideline. In the report no level is given. 2. No mentioning whether incubation was performed in darkness. According to the guideline, the test should be run in darkness. 3. Primary degradation is defined as "the alteration in the chemical structure of a substance, brought about by biological action, resulting in the loss of a specific property of that substance". As only the absorbance of the C-H stretch (CH_2-CH_3 band) is documented, other degradation-paths are not included. 4. The results represent primary biodegradation and should not be interpreted to reflect ready biodegradation. As such, the study is not considered useful, but can be seen as supporting data.	
Klimisch criterium	3 Primary biodegradation (notes 3 and 4)	

2.05

Title Aerobic Biodegradation Study of **CAS: 16958-92-2**

Date of report 12 January 1993.

GLP **No.**

Test substance CAS: 16958-92-2; purity = 100%.

Test method OECD 301 B; EPA 560/6-82-003

Test system

Treatment

- Inoculum: from activated sludge treatment at a Wastewater Treatment Plant. Amount inoculum 30 mg/l;
- 2 flasks Treated (medium + inoculum + CAS: 16958-92-2 (10 mg C/l));
- 2 flasks Positive Control (medium + inoculum + Rapeseed oil (10 mg C/l));
- >1 flask Blank Control (medium + inoculum).

Procedure Incubation was performed under continuous shaking in 2L flasks, containing 1 L of medium, test substance and/or inoculum. Inoculum and medium were not pre-acclimated before the test, but treated and aerated for 28 days at 25±3 ^{0}C with CO_2-free air. The outcoming air was passed through one CO_2-trap containing 10 ml 0.2N KOH. Flask traps were sampled at l-7 day intervals, depending on microbial activity. The amount of CO_2 was determined in the traps by backtitration with 0.2N HCl, after addition of $Ba(Cl)_2$ and indicator. One day prior to the final sampling (day 27), the medium was acidified with 1 ml concentrated sulphuric acid.

Results **Table** below Biodegradation values for **CAS: 16958-92-2** and positive control. Values are corrected for blank control values.

	Mean % biodegradation [% of $ThCO_2$] on day:					
Treatment	**2**	**5**	**9**	**14**	**22**	**29**
CAS: 16958-92-2	3.6	18	31	41	53	57
Positive control	16	57	68	74	79	79

Conclusion Not readily biodegradable.

Rev. note

1. Test was not performed in darkness, which will influence the results due to possible photodegradation of the test substance.
2. For CO_2 determination two or three absorber traps are normally used containing 100 ml base. In this test just one absorber trap was used containing 10 ml base, by which no ensurance can be given that all formed CO_2 can be trapped. An overflow of CO:! is expected when using one absorber trap.
3. CO_2 was trapped in potassium hydroxide in this test, but according to guideline 301 B it should be trapped in barium or sodium hydroxide. Backtitration was performed with 0.2N HCl instead of 0.05M HCl. These differences seem acceptable because it will not influence the results of the study.
4. In this test the reference compound used is rapeseed oil, which is not among the reference compounds advised to use by the guideline.
5. Minor remark: pH was not measured during the test.
6. *Minor* remark: The test was performed at a temperature exceeding the temperatures normally used. Micro-organisms might be influenced by this difference.
7. *Minor remark:* Amount of total CO_2 evolution in the inoculum blank was not indicated. For validity of the test this amount might normally not exceed 40 mg/l medium.
8. *Minor remark:* It is not clear how many replicates for the blank control were used; but it does meet the criteria (at least in duplicate).

Klimisch criterium 3 Additional yeast was added!

2.06

Title	Test for inhibition of oxygen consumption by activated sludge (EU guideline 87/302/EEC)
Date of report	October 6, 1997.
GLP	No.
Test substance	CAS: 16958-92-2, purity 100%.
Test method	87/302 EEC.
Stat. method	Not indicated.
Procedure	The test solution used in this study was an emulsification of the test substance with **CAS: aa** in water. The following treatments were included in the study: ▪ 3 treatment flasks (0.13, 1.3 and 13 g/L test substance/emulsifier (10/1 (w/w)) + inoculum) ▪ 2 positive control flasks (3.2 and 32 mg/L 3,5-dichlorphenol + inoculum) ▪ 2 control flasks (only inoculum) ▪ 1 control flask (1.3 g/L emulsifier + inoculum) ▪ 1 abiotic control flask (only test substance (13 g/L) + emulsifier) The inoculum used was activated sludge originated from a local sewage treatment plant. The oxygen consumption was measured after 3 hours at 20°C and pH 7.5.
Results	• No abiotic O_2 consumption • Respiration rates in control flasks with only inoculum were identical. • EC_{50} for 3,5-dichlorophenol 26 mg/l (3-h contact).
Conclusions	3-h EC_{50} >13 g/l.
Rev. note	Limited report. No information about nutrient solution used, aeration during the study, method of measurements inhibition, results for emulsifier control flask.
Klimisch criterium	2 Limited report.

2.07

Title	Department of Aquatic Toxicology Assessment of Ready Biodegradability using the CO_2 Evolution Test (Modified Sturm Test)
Date of report	26 April 1994.
GLP	**No.**
Test substance	CAS: 122-62-3, purity ~ 100%.
Test method	Not specified
Test system	**Treatment** ▪ Inoculum: from activated sludge from the aeration stage of a sewage treatment plant. Amount inoculum 10 ml/l (=1%). ▪ Blank control (medium + inoculum); ▪ Positive control (medium + inoculum + sodium benzoate (10 mg C/l)); ▪ Treated (medium + inoculum + **CAS:** 122-62-3 (20 mg C/l)). **Procedure** Incubation was performed in darkness under continuous stirring in vessels. The inoculum and medium were pre-acclimated during 24 hours, and subsequently treated and aerated for 29 days at 21-22°C with CO_2-free air. The outcoming air was passed through 2 consecutive CO_2-traps containing 350 ml 0.05 M NaOH. The amount of CO_2 was determined in the traps in duplicate by analysis on a Total Carbon Analyser on several days. pH was measured on day 28 in both vessels (pH = 7.4).

Results Table below Biodegradation values for **CAS:** 122-62-3 and positive control. Values are corrected for blank control values.

	Mean % biodegradation [% of $ThCO_2$] on day:														
Treatment	**1**	**2**	**3**	**6**	**8**	**10**	**12**	**14**	**16**	**20**	**22**	**24**	**27**	**28**	**29***
CAS: 122-62-3	0	3	10	29	38	49	55	55	59	60	60	64	66	65	66
Positive control	5	50	63	81	80	85	87	85	84	84	- -	89	90	87	87

● : Day 29 values corrected to include any carry-over of CO_2 detected in absorber 2 on Day 29.

Conclusion Not readily biodegradable (did not pass the 1 O-day window criterium according to OECD guideline 301 B).

Rev. note
1. No replicates were used, which makes results less reliable.
2. Test on toxicity control was performed according to OECD guideline 209; the test material did not exhibit any toxic effects on the inoculum at the concentrations employed in the test
3. The test substance is supposed to be almost readily biodegradable; at day 3 the test substance was degraded for 10% and at day 13 for 55% (1 O-day window).

Klimisch criterium **2**

2.08

Title Determination of the biodegradability of **"CAS: 28472-47-l"** by CEC L-33-T-82.

Date of report 21 December 1993.

GLP No.

Test substance CAS: 28472-47-l (purity not indicated)

Test method CEC L-33-T-82 (Biodegradability of two-stroke cycle outboard engine oils in water).

Test system

Treatments

For the test material:
1. nine flasks with medium + test/solvent solution (7.5 mg at the start) + inoculum.
2. four poisoned flasks with medium + test/solvent solution (7.5 mg at the start) + 1 ml of $HgCl_2$ (1% solution).

For the reference materials:
1. nine flasks with medium + reference/solvent solution (7.5 mg at the start) + inoculum.
2. four poisoned flasks with medium + reference/solvent solution (7.5 mg at the start) + 1 ml of $HgCl_2$ (1% solution).

Additionally, neutral flask(s) with medium + inoculum.

Flasks with the reference materials **(CAS: bb** and CAS: cc) were used to determine positive control. Abiotic degradation was determined in the poisoned flasks. The filtrate of sewage, collected at a municipal wastewater treatment plant, was used as inoculum.

Procedure Extraction with 1 ,1 ,2-trichlorotrifluoroethane under acidic conditions was performed on day 0 for the neutral flasks, 3 of the test and 3 of the reference flasks. The remaining flasks were incubated in the dark, at 20±1 °C with constant agitating. The primary biodegradation of the test and reference material was determined by quantitating the amount of unchanged material remaining in the flasks (2 poisoned flasks, 3 test and 3 reference flasks) at day 7 and day 21. This was done by Infrared Spectroscopy of the extracted test and reference solutions. The absorbance of the C-H stretch at 2931 cm^{-1} (CH_2-CH_3 absorbance band) was measured. Primary degradability was expressed as the percent difference in residual oil contents between the poisoned flasks and the respective test flasks.

Results After 7 days of incubation, 69% of test substance was biodegraded. For the reference material **CAS: bb,** this was 15.5%. For the reference material **CAS:** cc, this was 24%.

Conclusion Primary biodegradable (69% after 7 days).

Rev. note

1. The report is limited: the mineral medium and the treatments were not described in detail.
2. The guideline prescribes an incubation temperature of 25±1 "C. This study was performed at a temperature of 20±1 "C.
3. The calculations (residual oil content (%) and biodegradability (%)) do not follow the test guidelines. All the values given in the results are recalculated values.
4. Due to a failure in the test, the test results of the substance after 21 days were rejected (see page 14).
5. Primary degradation is defined as the alteration in the chemical structure of a substance, brought about by biological action, resulting in the loss of a specific property of that substance. As only the absorbance of the C-H stretch (CH_2-CH_3 band) is documented, other degradation-paths are not included.
6. The results represent primary biodegradation and should not be interpreted to reflect ready biodegradation. As such, the study is not considered useful, but can be seen as supporting data.

Klimisch criterium 3 Primary biodegradation (notes 5 and 6)

2.09

Title Determination of 'ready' biodegradability: carbon dioxide (CO_2) evolution test (Modified Sturm Test) with **CAS:** 103-24-2.

Date of report 10 July 1998.

GLP **Yes.**

Test substance CAS: 103-24-2, purity ~ not indicated by sponsor

Test method OECD 301/B (1992), 92/69/EEC L383, C.4-C (1992)

Test system

Treatment

- Inoculum: from activated sludge from a municipal sewage treatment plant;
- Test suspension: duplicate test substance (12 mg C/l) + inoculum;
- 1 flask positive control: sodium acetate (11.7 mg C/l) + inoculum;
- 2 flasks blank control: inoculum + medium;
- 1 flask toxicity control: test substance (12 mg C/l) + sodium acetate (11.7 mg C/l) + inoculum;

Amount inoculum 10 ml/l.

Procedure Incubation was performed under continuous stirring in brown 2 L glass flasks containing 2000 ml of mineral solution with test substance and/or The inoculum, mineral compounds and deionized water were pre-acclimated during one night, and subsequently treated and aerated for 28 days at 20±2°C with CO_2-free air. The outcoming air was passed through 3 consecutive Cop-traps containing 100 ml 0.0125N $Ba(OH)_2$. The amount of CO_2 was determined in the traps by backtitration of residual $Ba(OH)_2$ after 2, 5, 7, 9, 14, 19, 23, 27 and 29 days. On the 28'" day HCI was added to the bottles, whereafter final titration was performed.

Results **Table below** Gives biodegradation values for **CAS: 103-24-2** (two replicates), toxicity control and positive control. Values are corrected for blank.

	Mean % biodegradation [% of $ThCO_2$] on day:								
Treatment	**2**	**5**	**7**	**9**	**14**	**19**	**23**	**27**	**29**
CAS: 103-24-2 (A)	1.1	7.8	9.5	25	53	70	81	84	89
CAS: 103-24-2 (B)	0.0	5.8	30	46	66	72	72	72	73
Toxicity control	0.0	6.1	20	33	57	71	75	78	79
Positive control	2.3	20	29	42	86	91	96	97	97

Conclusion Readily biodegradable.

Rev. note No remarks.

Klimisch Criterium 1

2.10

Title	Determination of the biodegradability of "CAS: 28472-97-1" by CEC L-33-T-82.
Date of report	21 December 1993.
GLP	No.
Test substance	CAS: 28472-97-l (purity not indicated)
Test method	CEC L-33-T-82 (Biodegradability of two-stroke cycle outboard engine oils in water).
Test system	**Treatments** For the test material: 1. nine flasks with medium + test/solvent solution (7.5 mg at the start) + inoculum. 2. four poisoned flasks with medium + test/solvent solution (7.5 mg at the start) + 1 ml of $HgCl_2$ (1% solution). For the reference materials: 1. nine flasks each with medium + reference/solvent solution (7.5 mg at the start) + inoculum. 2. four poisoned flasks each with medium + reference/solvent solution (7.5 mg at the start) + 1 ml of $HgCl_2$ (1% solution). Additionally, neutral flask(s) with medium + inoculum. Flasks with the reference materials **(CAS: bb** and **CAS:** cc) were used to determine positive control. Abiotic degradation was determined in the poisoned flasks. The filtrate of sewage, collected at a municipal wastewater treatment plant, was used as inoculum. **Procedure** Extraction with 1 ,1,2-trichlorotrifluoroethane under acidic conditions was performed on day 0 for the neutral flasks, 3 of the test and 3 of the reference flasks. The remaining flasks were incubated in the dark, at 20±1 °C with continuous agitating. The primary biodegradation of the test and reference material was determined by quantitating the amount of unchanged material remaining in the flasks (2 poisoned flasks, 3 test and 3 reference flasks) at day 7 and day 21. This was done by Infrared Spectroscopy of the extracted test and reference solutions. The absorbance of the C-H stretch at 2931 cm^{-1} (CH_2-CH_3 absorbance band) was measured. Primary degradability was expressed as the percent difference in residual oil contents between the poisoned flasks and the respective test flasks.
Results	After 7 days of incubation, 72% of test substance was biodegraded. For the reference material **CAS: bb,** this was 15.5%. For the reference material **CAS:** cc, this was 24%.
Conclusion	Primary biodegradable (72% after 7 days).
Rev. note	1. The report is limited: the mineral medium and the treatments were not described in detail. 2. The guideline prescribes an incubation temperature of 25±1°C. This study was performed at a temperature of 20±1°C. 3. The calculations (residual oil content (%) and biodegradability (%)) do not follow the test guidelines. All the values given in the results-section are recalculated values. 4. Due to a failure in the test, the test results of the substance after 21 days were rejected (see page 14). 5. Primary degradation is defined as "the alteration in the chemical structure of a substance, brought about by biological action, resulting in the loss of a specific property of that substance". As only the absorbance of the C-H stretch (CH_2-CH_3 band) is documented, other degradation-paths are not included. 6. The results represent primary biodegradation and should not be interpreted to reflect ready biodegradation. As such, the study is not considered useful, but can be seen as supporting data.
Klimisch Criterium	3 Primary biodegradation (notes 5 and 6)

GROUP C

2.11

Title Ready Biodegradability: Modified Sturm Test, 40 CFR 796.3260 **CAS: Mix of 67989-24-6 and 70024-57-6**

Date of report October 1992.

GLP No.

Test substance CAS: mix of 67989-24-6 and 70024-57-6; purity not indicated.

Test method Modified Sturm Test

Test system **Treatment** - Inoculum: from fresh activated sludge from a public owned treatment works. Microbial density 6.1'1 0^3 CFU/ml;

- 1 flask Treated (medium + inoculum **+ mix of 67989-24-6 and** 70024-57-6 (7.8 mg C/l));
- 1 flask Treated (medium + inoculum **+ mix of 67989-24-6 and** 70024-57-6 (15.6 mg C/l));
- 1 flask Positive Control (medium + inoculum + sodium acetate (20 mg/l acetate));
- 1 flask Negative Control (medium + inoculum).

Procedure Incubation was performed in 3L test vessels containing medium, test substance and/or inoculum. Inoculum and medium were purged with CO_2-free air during 24 hours. The test system, containing 4 vessels, was operated for 34 days at 21 ± 2^0C, under a constant gas flow. The outcoming air was passed through CO_2-traps containing $Ba(OH)_2$ solutions. The amount of CO_2 produced during the course of the test was monitored.

Results **Table below** Biodegradation values for **CAS: Mix of 67989-24-6 and 70024-57-6** (low and high concentrations) and positive control. Unclear whether values were corrected for negative control values.

	Mean % biodegradation [% of $ThCO_2$] on day:														
Treatment	**0**	**2**	**5**	**7**	**9**	**12**	**15**	**18**	**22**	**25**	**28**	**30**	**32**	**34**	**37**
Test substance (7.8 mg C/l)	0.0	5.1	23	39	42	49	58	64	68	68	68	69	72	72	73
Test substance (15.6 mg C/l)	0.0	7.2	27	48	53	60	67	72	76	77	78	79	80	80	82
Mean value	0.0	6.2	25	44	48	55	63	68	72	73	73	74	76	76	78
Positive control	0.0	18	33	46	50	55	67	77	83	83	85	85	86	86	87

Conclusion **CAS: Mix of 67989-24-6 and 70024-57-6** is ready biodegradable.

Rev. note

1. Limited report, no information on:
   - Light regime;
   - Stirring regime;
   - Amount of inoculum;
   - pH regime;
   - Test medium;
   - Number of absorption bottles and the volume of $Ba(OH)_2$ used;
   - The way of determination of CO_2-amount in the absorption traps:
   - Amount of total CO_2 evolution in the inoculum blank.
2. No replicates for treated flasks and inoculum blank flasks were used, which makes results less reliable.

Klimisch Criterium 2 Limited report.

2.12

Title Ready biodegradability: Modified OECD screening test according to OECD screening test

Date of report September 6, 1991.

GLP **Yes.**

Test substance CAS: 70729-68-g; Tetraethylene Glycol Diheptanoate (TGD); purity: 95%.

Test method OECD 301 E; EEC 79/831.

Test system

Treatment
- Sample: mineral nutrient solution + inoculum + TGD (≡ 47.3 mg DOC/L);
- Positive control: mineral nutrient solution + inoculum + sodium benzoate (≡ 20 mg DOC/L);
- Blank control: mineral nutrient solution + inoculum.

The amount of flasks was not indicated.

Procedure Aliquots of a stock solution of the test substance (tested concentration 74.9 mg/l providing 47.3 mg DOC/L), inoculum from an treatment plant (secondary effluent) and mineral nutrient solution (1.5 mL) were mixed. Water was added to give a final volume of 1.5 L. The test mixture (it was not indicated that the test was performed in duplicate) was incubated at 22 ± 1 °C for 32 days being shielded from light (pH (t=O) 7.2-7.8). Aeration was accomplished by diffusion facilitated by shaking (120 rpm). Samples were taken on days 0, 7, 14, 21 and 28. For DOC-determination, samples were centrifuged and analysed in duplicate for TC (total carbon) and IC (inorganic carbon), whereafter the DOC was calculated.

Results **Table below** Biodegradation values for test article Tetraethylene Glycol Diheptanoate (TGD) and positive control.

	% biodegradation on day:				
Treatment	**0**	**7**	**14**	**21**	**28**
TGD	0	49	**72**	**92**	**98**
Positive control	(O	91	91	90	100

Conclusion Biodegradable.

Rev. note
1. In the mineral nutrient solution two components were replaced by other components ($MnCl_2$ instead of $MnSO_4$; yeast extract instead of vitamin solution). However it is anticipated that this replacement will not influence the results.
2. The DOC of test substance (47 mg DOC/L) exceeded the prescribed amount of IO-40 mg DOC/L.
3. No sufficient samples were taken in the 10-day window. However, this deviation seems acceptable since a high biodegradation percentage was reached in a very short time.
4. The amount of flasks used for each test solution was not indicated. It is anticipated that no duplicates were used. This results in a less reliable study.
5. No information on the concentration of secondary effluent was given; should be 0.5 mL/L mineral medium.

Klimisch Criterium 2 Note 4 and 5.

GROUP D

2.13

Title Biodegradability of **"CAS: 1338-43-8"**

Date of report May 4, 1988.

GLP **No.**

Test substance CAS: 1338-43-8, purity nor indicated.

Guideline Not indicated.

Test system Not specified.

Results Residual organic carbon at end of the test: **CAS:** 1338-43-8, 98.2%; Aniline, 97.4%.

	Mean % biodegradation [% of COD] on day:					
Treatment	**5**	**10**	**15**	20	25	28
CAS: 1338-43-8	**29**	43	54	56	61	62
Positive control (Aniline)	39	46	56	61	64	66

Conclusion Not readily biodegradable

Rev. note
1. Only the result of a biodegradability study was available.
2. Study seems not valid, positive control shows only 56% degradation after 15 days (OECD 301, ≥60% within 14 days).
3. COD is used instead of ThOD. When using the COD the biodegradability can be overestimated.

Klimisch criterium 4 Incomplete report (note 1), validity (note 2).

2.14

Title **CAS: 1338-39-2:** Biodegradability

Date of report March 22, 1984.

GLP Yes.

Test substance CAS: 1338-39-2; purity ~ not indicated.

Test method OECD 301C (1981).

Test system **Treatment**
- Inoculum: activated sludge;
- 1 flask Treated (medium + inoculum + **CAS: 1338-39-2 (62** mg C/l));
- 1 flask Positive Control (medium + inoculum + aniline).

Procedure The test substance was stirred in an aqueous medium (100 mg/l) with activated sludge (30 mg/l) for a period of 28 days. During this period BOD was measured and at the end of the period the level of organic carbon, remaining in the aqueous phase, was measured.

Results **Table below** Gives biodegradation values for CAS: 1338-39-2 and positive control. Values are not corrected for blank values.

	Mean % biodegradation [% of COD] on day:					
Treatment	5	**10**	**15**	20	25	28
CAS: 1338-39-2	**51**	56	59	60	59	60
Positive control	39	46	56	61	64	66

Conclusion Not readily biodegradable, but significantly biodegradable (failed the IO-day window).

Rev. note
1. The positive control did not reach the pass level of 60% degradation by day 14, which causes the study to be invalid. The test substance was shown to be more biodegradable than the positive control.
2. According to OECD guidelines the main criteria for ready biodegradability is the 1 O-day window. This test report refers to another criterion for ready biodegradability: >60% conversion to CO_2 in 28 days. This is not in accordance with the OECD guidelines; this summary is based on the OECD guidelines.
3. Incomplete description, no information on:
- Which amount and which source of inoculum were used;
- Which concentration of aniline in positive control was used;
- Which medium was used.
- Replicates, which makes results less reliable and does not meet the criteria as mentioned in OECD 301 guidelines.
- pH of the contents of the bottles at the end of the test. pH values of treated flask was not adjusted before inoculation.
- Performance of a few observations, as described in OECD guidelines (e.g. colour changes of contents in vessel).
4. Test was not performed in darkness, which might influence test results due to possible photodegradation of the test substance and is therefore less reliable.
5. Two tests have not been performed, which are requested in the guidelines: i) test substance + water + inoculum and ii) medium + inoculum. These make the test incomplete.

Klimisch criterium 4 Instead of the $ThCO_2$ the COD was used. Although this is acceptable, this results in an overestimation of the biodegradation value.

GROUP E

2.15

Title	Biodegradability Test for Synthetic Esters
Date of report	1987.
GLP	Not specified.
Test substance	CAS: 14450-05-6; CAS: 126-57-8, purity not indicated.
Test method	Not indicated.
Test system	**Treatment** Not indicated. **Procedure** Various synthetic esters were tested for their biodegradability, using a test sequence that began with the creation of biomass using sucrose and municipal wastewater. Subsequently the micro-organisms were adapted to the concerning test substances. Finally the ester was tested with the micro-organisms. The test was carried out in batches for seven days at 20 ± 0.2 ºC in the dark.
Rev. note	No conclusion and no results were included in this summary, due to the poor test description in the report. In addition, the test itself was performed very poorly: The test was only performed for 7 days, instead of (at least) 28 days and adapted micro-organisms were used.
Klimisch Criterium	3

2.16

Title	Aerobic Biodegradation Study of **CAS:** 67762-53-2; 67762-52-l
Date of report	May 18, 1992.
GLP	**No.**
Test substance	CAS: 67762-53-2; 67762-52-l ; purity not indicated.
Test method	OECD 301 B; EPA 560/6-82-003
Test system	**Treatment** - Inoculum: prepared from soil and from activated sludge obtained from a municipal treatment plant (25 ml). - 2 flasks Treated (modified medium + inoculum + **CAS:** 67762-53-2; **67762-52-l** (10 mg C/l)); - 2 flasks Positive Control (modified medium + inoculum + Rapeseed oil (10 mg C/l)); - 2 flasks Blank Control (composition not specified; rev. note); - In addition, each flask received 1 ml of yeast extract solution. **Procedure** Incubation was performed under continuous shaking in 2L flasks. Inoculum was not pre-acclimated before the test, but treated and aerated at 25±3 ^{0}C with CO_2-free air. The outcoming air was passed through one CO_2-trap containing 10 ml 0.2N KOH. Flask traps were sampled at 1-7 day intervals, depending on microbial activity. The amount of CO_2 in the traps was determined by backtitration with 0.2N HCl, after addition of $BaCl_2$ and indicator. One day prior to the final sampling, the medium was acidified with 1 ml concentrated sulphuric acid.

Results **Table below** Biodegradation values for **CAS:** 67762-53-2; 67762-52-l and positive control. Values are corrected for blank control values.

		Mean % biodegradation [% of $ThCO_2$] on day:					
Treatment	2	5	9	15	21	28	33
CAS: 67762-53-2; 67762-52-l	0.3	1.6	1.6	2.6	2.6	5.2	12
Positive control	23	62	77	a2	a4	a4	a4

Conclusion Not readily biodegradable.

Rev. note

1. An insufficient number of CO_2 samples was taken. According to the guideline samples should be taken every second or third day during the first ten days and every fifth day until the 28h day.
2. CO_2 was trapped in potassium hydroxide in this test, but according to guideline 301 B it should be trapped in barium or sodium hydroxide. Backtitration was performed with 0.2N HCl instead of 0.05M HCl. These deviations seem acceptable as they are expected not to influence the results of the study.
3. Test was not performed in darkness, which will influence the results due to possible photodegradation of the test substance.
4. For CO_2 determination two or three absorber traps are normally used containing 100 ml base. In this test just one absorber trap was used containing 10 ml base, by which no ensurance can be given that all formed CO_2 can be trapped. Break-through of CO_2 cannot be excluded when using only one absorber trap.
5. In this test the reference compound used is rapeseed oil, which is not among the reference compounds advised to use by the guideline.
6. Amount of total CO_2 evolution in the blank control was not indicated. For validity of the test this amount might normally not exceed 40 mg/l medium. Blanks were not described in the report.
7. The test was not performed with a toxicity control; acceptable in worst case approach.
a. Yeast is added in this test. Since yeast is bio-active, it is not acceptable.
9. Soil inoculum defined as soil #104. No further information included in report.
10. *Minor remark:* pH was not measured during the test.
11. *Minor remark:* The test was performed at a temperature exceeding the temperatures as indicated by the guideline. Activity of micro-organisms may be influenced by this difference.

Klimisch criterium 3

2.17

Title Aerobic Biodegradation Study of **CAS: 11138-60-6**

Date of report February 3, 1993.

GLP **No.**

Test substance CAS: 11138-60-6; purity = 100%.

Test method OECD 301 B; EPA 560/6-82-003

Test system **Treatment** -
- Inoculum: from activated sludge treatment at a Wastewater Treatment Plant.
- 2 flasks Treated with low concentration (medium + inoculum + **CAS: 11138-60-6** (10 mg C/l));
- 2 flasks Treated with high concentration (medium + inoculum + **CAS: 11138-60-6 (20** mg C/l));
- 2 flasks Positive Control (medium + inoculum + sodium benzoate (20 mg C/l));
- 2 flasks Blank Control (medium + inoculum).

Procedure Incubation was performed under continuous shaking in 2L flasks, containing 1L of medium, test substance and/or inoculum. Inoculum and medium were not pre-acclimated before the test. They were treated and aerated for 28 days at 25±3°C with CO_2-free air. The outcoming air was passed through one CO_2-trap containing 10 ml 0.2N KOH. Flask traps were sampled at l-7 day intervals, depending on microbial activity. The amount of CO_2 was determined in the traps by backtitration with 0.2N HCl, after addition of $Ba(Cl)_2$ and indicator. One day prior to the final sampling (day 27), the medium was acidified with 1 ml concentrated sulphuric acid.

Results **Table** below Biodegradation values for **CAS: 11138-60-6** (low and high concentrations) and positive control. Values are corrected for blank control values.

	Mean % biodegradation [% of $ThCO_2$] on day:					
Treatment	**2**	**5**	**9**	**14**	**21**	**27**
CAS: 11138-60-6 (10 mg C/l)	5.0	34	53	58	64	67
CAS: 11138-60-6 (20 mg C/l)	6.7	38	54	58	62	64
Positive control	47	77	83	84	87	90

Conclusion Not readily biodegradable.

Rev. note

1. Test substance is biodegradable and almost meets the 1 O-day window criteria (almost readily biodegradable).
2. Yeast is added in this test. Since yeast is bio-active, it is not acceptable.
3. Test was not performed in darkness, which will influence the results due to possible photodegradation of the test substance.
4. For CO_2 determination two or three absorber traps are normally used containing 100 ml base. In this test just one absorber trap was used containing 10 ml base, by which no ensurance can be given that all arising CO_2 can be measured. An overflow of CO_2 is expected when using only one absorber trap.
5. The amount of inoculum used has not been specified; it cannot be concluded whether the concentration used meets the guideline criteria.
6. CO_2 was trapped in potassium hydroxide in this test, but according to guideline 301 B it should be trapped in barium or sodium hydroxide. Backtitration was pet-formed with 0.2N HCl instead of 0.05M HCl. These differences seem acceptable because it will not influence the results of the study.
7. Minor remark: pH was not measured during the test.
8. *Minor* remark: The test was performed at a temperature exceeding the temperatures normally used. Micro-organisms might be influenced by this difference.
9. *Minor remark:* Amount of total CO_2 evolution in the inoculum blank was not indicated. For validity of the test this amount might normally not exceed 40 mg/l medium.
10. *Minor remark:* Test medium deviates from OECD guideline. Two additional solutions were used. These deviations are not expected to make the results less reliable.

Klimisch Criterium 3 Additional yeast was added!

2.18

Title	CEC test for biodegradation study of **CAS: 11138-60-6.**	
Date of report	April 12, 1994.	
GLP	No.	
Test substance	CAS: 11138-60-6 (purity not indicated)	
Test method	CEC L-33-T-82 (Biodegradability of two-stroke cycle outboard engine oils in water).	
Test system	**Treatments**	For the test material: 1. nine flasks with 150 ml CEC test medium + test/solvent solution (50 mg/l end concentration) + 1 ml inoculum 2. four poisoned flasks with 150 ml CEC test medium + test/solvent solution (50 mg/l end concentration) + 1 ml of $HgCl_2$ (10g/l solution). For the reference material: 1. nine flasks with 150 ml CEC test medium + reference/solvent solution (50 mg/l end concentration) + 1 ml inoculum 2. four poisoned flasks with 150 ml CEC test medium + reference/solvent solution (50 mg/l end concentration) + 1 ml of $HgCl_2$ (1 0g/l solution). Additionally, two neutral flasks with 150 ml CEC test medium + 1 ml inoculum. Flasks with the reference material **(CAS: zz**) were used as positive control. Abiotic degradation was determined in the poisoned flasks. The supernatant of mixed liquor, collected at a municipal wastewater treatment plant, was used as inoculum.
	Procedure	Extraction with Freon 113 under acidic conditions was performed on day 0 for the neutral flasks, 3 of the test and 3 of the reference flasks. The remaining flasks were incubated in a rotary incubator, at 25±3°C with continuous agitating (150 rpm). The primary biodegradation of the test and reference material was determined by quantitating the amount of unchanged material remaining in the flasks (2 poisoned flasks, 3 test and 3 reference flasks) at day 7 and day 21. This was done by Fourier Transform Infrared Spectroscopy of the extracted test and reference solutions. The absorbance of the C-H stretch at 2930 cm^{-1} (CH_2-CH_3 absorbance band) was measured. Primary degradability was expressed as the percent difference in residual oil contents between the poisoned flasks and the respective test flasks.
Results	After 7 days of incubation, more than 95% of the test substance was biodegraded. For the reference material, 61% was biodegraded in 21 days.	
Conclusion	Good primary biodegradability (> 95%).	
Rev. note	1. No count was done of the colonies in the inoculum. The bacteria level of the inoculum should be $\geq 10^6$ CFU/ml according to the guideline. In the report no level is given. 2. No mentioning was done whether incubation was performed in darkness. According to the guideline, the test should be run in darkness. 3. Primary degradation is defined as "the alteration in the chemical structure of a substance, brought about by biological action, resulting in the loss of a specific property of that substance". As only the absorbance of the C-H stretch (CH_2-CH_3 band) is documented, other degradation-paths are not included. 4. The results represent primary biodegradation and should not be interpreted to reflect ready biodegradation. As such, the study is not considered useful, but can be seen as supporting data.	
Klimisch criterium	3 Primary biodegradation (notes 3 and 4)	

2.19

Title	Test substance: **CAS: 11138-60-6** Physical/chemical testing for CEPA regulations; 3. Adsorption/desorption.
Date **of report**	August 30, 1996.
GLP	No.
Test substance	CAS: 11138-60-6; multicomponent mixture.
Test method	OECD 106.
Procedure	Three soils (pH 5.1, 3% clay content, 1.9% organic matter; pH 5.7, 25% clay content, 0.4% organic matter; pH 9.0, 30% clay content, 7.8% organic matter) were tested. Equilibration was performed with 2.0 gram of soil and 10 mL of 0.01 M aqueous calcium chloride solution for 24 hours at 22°C (triplicate samples in polypropylene tubes). A spike solution of the test substance in acetonitrile was made (254.0 µg/mL). *Definitive* test 10.0 µL of spike solution was added to two samples per soil, while the third sample was not spiked to serve as blank. The contents of the tubes were mixed for 16 hours, then centrifuged and the supernatants were decanted. After addition of calciumchloride solution and resuspension of the soil, the contents were mixed for 22.2 hours, centrifuged and the supernatant decanted. This procedure was repeated once, with a mixing time of 23.6 hours. Supernatants were kept in the freezer until analysis. The calcium chloride solutions sampled were extracted with 2 mL of methyl *t.*-butyl ether and one µL of the extract was analysed by GC-FID. In addition, during the adsorption step, quantitation standards were run along containing 10 mL calcium chloride solution and various amounts (2-l 0 µL) of spike solution. The temperature of the experiment was 22 ±1 °C.
Results	The lowest detectable concentration of **CAS: 11138-60-6** was estimated at 0.1 µg/mL. The linear regression of the calibration curve was 0.95. No **CAS: 11138-60-6** was detected in the adsorption solutions and in the two desorption solutions for the three soils tested. Therefore, > 61% of **CAS: 11138-60-6** adsorbed to the three soils and < 39% of the adsorbed **CAS: 11138-60-6** desorbed from the three soils.
Conclusion	> 61% adsorbed to the three soils and < 39% desorbed from the three soils.
Rev. note	1. The two desorption steps of the study should have lasted only 16 hours each instead of 22.2 and 23.6 hours. However, as after this prolonged desorption time still no desorption could be detected above the limit of detection, this deviation from the guideline is acceptable. 2. No information was given whether the soils were sieved prior to use. It was stated in the report that further soil characterisation data were in the APPENDIX. However, the report submitted to the reviewer did not contain an APPENDIX. 3. No analysis was performed to establish the stability of the test substance under the test conditions (at the end of the experiment). As the test substance is an ester that is put into contact with acidic and basic soils, hydrolysis may be expected. No mass balance was established either (although this is only required for an advanced test). Thus, the apparent high degree of adsorption may also have been caused by the fact that the test substance was destroyed. 4. Possible adsorption of the test substance to the container walls was not addressed. Although (one of) the quantitation standards could have served as control sample, they were not used as such.
Klimisch criterium	3 Stability of test substance under test conditions questionable (note 3).

2.20

Title	Test for inhibition of oxygen consumption by activated sludge (EU guideline 87/302/EEC)
Date of report	October 6, 1997.
GLP	No.
Test substance	CAS: 11138-60-6, purity 100%.
Test method	871302 EEC.
Stat. method	Not indicated.
Procedure	The test solution used in this study was an emulsification of the test substance with Tween 80 in water. The following treatments were included in the study: - 3 treatment flasks (0.13, 1.3 and 13 g/L test substance/emulsifier (10/1 (w/w)) + inoculum) - 2 positive control flasks (3.2 and 32 mg/L 3,5-dichlorophenol + inoculum) - 2 control flasks (only inoculum) - 1 control flask (1.3 g/L emulsifier + inoculum) - 1 abiotic control flask (only test substance (13 g/L) + emulsifier) The inoculum used was activated sludge originated from a local sewage treatment plant. The oxygen consumption was measured after 3 hours at 20°C and pH 7.5.
Results	• No abiotic O_2 consumption • Respiration rate in control flasks with only inoculum were identical. • EC_{50} for 3,5-dichlorophenol 26 mg/l (3-h contact).
Conclusions	3-h EC_{50} >13 g/l.
Rev. note	Limited report. No information about nutrient solution used, aeration during the study, method of measurements inhibition, results for emulsifier control flask.
Klimisch criterium	2 Limited report (note 1).

2.21

Title	Determination of the Aerobic Ready Biodegradability of **CAS: 11138-60-6** using the OECD 301 B CO:! Evolution (Modified Sturm) Test Method
Date of report	November 26, 1996.
GLP	Yes.
Test substance	CAS: 11138-60-6, trimethylolpropane caprylate caprate), purity ~ 100%.
Test method	OECD 3018 (1992), 92/69/EEC L383, C4 (1992).
Test system	**Treatment** - Inoculum: from activated sludge from a municipal wastewater treatment plant. Amount inoculum 7 ml/l. - Treated (2 flasks): medium + inoculum + test substance (20 mg C/l); - Positive control (2 flasks): medium + inoculum + sodium benzoate (20 mg C/l); - Blank control (2 flasks): inoculum (without test- and control substance). **Procedure** Incubation was performed under continuous stirring in 4 L glass bottles containing 3000 ml of medium with test substance and/or inoculum. The inoculum was not pre-acclimated. It was treated and aerated for 28 days in the dark at 23-24°C with CO_2-free air. The outcoming air was passed through 3 consecutive absorber CO_2-traps containing 0.0126 M $Ba(OH)_2$. CO_2 was determined in the traps by backtitration of residual $Ba(OH)_2$ with standardised 0.05 M HCl after 1, 3, 5, 6, 10, 14, 21 and 28 days. On day 29 determination of the amount of carbon dioxide evolved in the remaining trap bottles was carried out.
Results	**Table below** Gives biodegradation values for **CAS: 11138-60-6** and positive control, corrected for blank (average of 2 Sturm bottles).

		Mean % biodegradation [% of $ThCO_2$] on day:					
Treatment	1	**3**	**6**	**10**	**14**	**21**	**28**
CAS: 11138-60-6	**0.0**	11	29	**45**	**54**	**61**	**76**
Positive control	5.9	**26**	**46**	**65**	71	75	78

Conclusion	Not readily biodegradable (failed the 10-day window), but significant degradation.
Rev. note	No remarks.
Klimisch Criterium	1

2.22

Title Comparison of the Ready and Ultimate Biodegradability of Seven Oleochemicals

Date of report November 20, 1995.

GLP No.

Test substance CAS: 11138-60-6 (Trimethylolpropanetriester of C8/C10 (1 :1) fatty acids), purity not applicable.

Test method Sealed Vessel Test based on OECD 301 B (1981).

Test system

Treatment

- Inoculum: secondary effluent from an unacclimatised activated sludge plant at URL North. Amount inoculum: 10 v/v%;
- 12 flasks Treated (medium + inoculum **+ CAS: 11138-60-6, (9.98** mg C/l);
- 12 flasks Blank Control (medium + inoculum);
- 12 flasks Positive Control (medium + inoculum + sodium benzoate (10 mg C/l)).

Procedure Incubation was performed during 28 days on a rotary shaker at 20°C (17-24°C) in sealed vessels (160 ml), containing 100 ml mineral medium and inoculum. At 3-4 day intervals during the test period a vessel was removed, whereafter the concentration of carbon dioxide in the headspace gas was determined and also the concentration of inorganic carbon in the test medium. Analysis of both headspace gas and the liquid medium was performed with an inorganic Carbon Analyser. On day 3, 7, 10, 14, 17, 21 and 24 one vessel per treatment was analysed. On day 28, five vessels were analysed.

Results **Table below** Gives biodegradation values for **CAS: 11138-60-6** and positive control. Values are corrected for blank.

		Mean % biodegradation [% of $ThCO_2$] on day:						
Treatment	3	7	**10**	**14**	**17**	**21**	24	28
CAS: 11138-60-6	**16**	38	61	77	93	69	78	75
Positive control	55	86	93	95	101	97	106	97

Conclusion Readily biodegradable.

Rev. note

1. It cannot be concluded whether the following experimental conditions meet the guideline criteria, as the test report does not specify them:
   - medium used;
   - whether the test was performed in darkness. When not performed in darkness, photodegradation of the substances might take place.
2. *Minor* remark: Variation in temperature was too wide, which makes results less reliable.
3. Minor **remark:** Vessels used were too small; volume of a vessel should be at least 2L.

Klimisch Criterium 2

2.23

Title Determination of 'ready' biodegradability: carbon dioxide (CO_2) evolution test (Modified Sturm Test) with **CAS:** 57675-44-2 and analytical chemical comparison of **CAS: 57675-**44-2 with **CAS: dd** and **CAS: ee**

Date of report December 5, 1995.

GLP **Yes.**

Test substance CAS: 57675-44-2; purity not indicated (treated as 100% pure in this test).

Test method OECD 301/B (1992), 92/69/EEC L383, C.4-C (1992)

Test system

Treatment

- Inoculum: from activated sludge from a municipal sewage treatment plant. Amount inoculum 10 ml/l.
- 2 flasks Treated (medium + inoculum + test substance (15 mg C/l));
- 1 flask Positive control (medium + inoculum + sodium acetate (11.7 mg C/l));
- 2 flasks Blank control (medium + inoculum);
- 1 flask Toxicity control (medium + inoculum + test substance (15.4 mg C/l), sodium acetate (11.7 mg C/l)).

Procedure Incubation was performed under continuous stirring in brown 2 L brown glass bottles. The inoculum and medium were pre-acclimated during one night, and subsequently treated and aerated for 28 days at 21-23°C with CO_2-free air. The outcoming air was passed through 3 consecutive Cop-traps containing 100 ml 0.0125N $Ba(OH)_2$. The amount of CO_2 was determined in the traps by backtitration of residual $Ba(OH)_2$ with 0.05 M HCl after several days. On the 28'" day HCl was added to the bottles, whereafter final titration was performed on day 29. pH was monitored just before the start of the test and on day 28 and varied from 7.4 to 8.0.

Results **Table below** Gives biodegradation values for **CAS:** 57675-44-2 (two replicates (A, B)), toxicity control and positive control. Values are corrected for blank.

	Mean % biodegradation [% of $ThCO_2$] on day:									
Treatment	**3**	**5**	**7**	**10**	**14**	**17**	**21**	**24**	**27**	**29**
CAS: 57675-44-2 (A)	4.1	9.6	19	29	56	67	75	78	80	88
CAS: 57675-44-2 (B)	6.3	15	22	33	58	65	71	74	76	82
Toxicity control	4.0	8.3	22	32	48	57	63	67	68	70
Positive control	19	35	50	62	70	73	76	81	84	97

Conclusion Not readily biodegradable (failed the 1 O-day window), but significant degradation.

Rev. note

1. **CAS:** 57675-44-2 was found to be not inhibitory in the toxicity control.
2. *Minor remark:* slight deviation in temperature; no influence on results of test expected.

Klimisch Criterium 1

2.24

Title Ready Biodegradability: Modified Sturm Test with **CAS:** 126-57-8.

Date of report August 8, 1991.

GLP Yes.

Test substance CAS: 126-57-8, purity ~ 100%.

Test method OECD 301/B (1981), 84/449/EEC L251, C5 (1984)

Test system

Treatment

- Inoculum: from activated sludge from a municipal sewage treatment plant. Amount inoculum 10 ml/l (1%).
- Treated (medium + inoculum + test substance (low: 7,1 mg C/l and high: 14,3 mg C/l)).
- Positive control (medium + inoculum + sodium acetate (20 mg/l □ 5,9 mg C/l));
- Blank control (medium + inoculum (without test- and control substance)).

Procedure Incubation was performed under continuous stirring in brown 3 L glass flasks containing 3000 ml of mineral solution with test substance and/or inoculum. The inoculum was pre-acclimated for 24 h, treated and aerated for 28 days at 20±2°C with CO_2-free air. The outcoming air was passed through 3 consecutive CO_2-traps containing 0.025N $Ba(OH)_2$. CO_2 was determined in the traps by backtitration of residual $Ba(OH)_2$ at several days. Samples of the incubate were removed on day 26 for DOC analysis.

Results

Analysis Not reported

DOC

Table below Gives biodegradation values for **CAS:** 126-57-8 and control treatment, the values are corrected for blank.

	Mean % biodegradation [% of $ThCO_2$] on day:							
Treatment	**2**	**5**	**7**	**9**	**12**	**16**	**21**	**28**
CAS: 126-57-8 (10 mg/l)	0.0	4.3	13	17	22	29	36	43
CAS: 126-57-8 (20 mg/l)	0.0	1.2	16	27	37	45	51	54
Positive control	6.2	17	24	28	37	61	96	111*

● : due to acidification

Conclusion Not readily biodegradable.

Rev. note

1. Composition nutrient solution not in accordance with OECD 301 B.
2. No replicate flasks included.
3. Positive control degrades, but probably not within 14 days. Due to this the test is less reliable.
4. Not enough CO2 samples were taken at the end of the test.

Klimisch Criterium **2**

2.25

Title Schedule II notification related studies for CAS: 126-57-8; 1. Adsorption/Desorption

Date of report July 24, 1997.

GLP No.

Test substance CAS: 126-57-8; trimethylolpropane tripelargonate, purity 100%.

Test method Not indicated

Procedure 40 mL of ultrapure water and 2 mL of **CAS:** 126-57-8 were vigorously mixed for 30 minutes at 23°C to obtain an essentially saturated aqueous solution. After centrifugation and equilibration, the aqueous phase was separated and extracted with methyl *t*.-butyl ether after which the extract was analysed by GC-FID. This alternative method gave the same result for the water solubility as the method described in 9.1.19, namely a water solubility of 8.4 mg/L at 23°C. Based on this result and the lowest detectable concentration, it was assumed that the concentrations of **CAS: 126-**57-8 in the adsorption test would be too low to determine with acceptable accuracy. Therefore the extent of adsorption was estimated by comparison with a similar substance, **CAS:** ff. This substance differed from **CAS: 126-57-8** in that **CAS:** 126-57-8 contained two additional methylene groups on each alkyl side chain. It was expected that **CAS:** 126-57-8 would be more hydrophobic and less water soluble than **CAS:** ff. It follows that **CAS:** 126-57-8 would adsorb to soil to the same extent or greater than **CAS: ff.** Therefore, it was expected that the adsorption results for **CAS:** ff (minima) would also apply to **CAS: 126-57-8**.

Results > 72% of **CAS:** ff adsorbed to the three soils investigated (see note 1) and < 25% of the adsorbed **CAS:** ff desorbed from the three soils.

Conclusion

Rev. note

1. No information on test procedure for **CAS:** ff was given. This was reported in an addendum report not available to the reviewer. Three soils (pH 5.1, 3% clay content, 1.9% organic matter: pH 5.7, 25% clay content, 0.4% organic matter; pH 9.0, 30% clay content, 7.8% organic matter) were tested.
2. As the test substance **CAS: ff** is an ester that was put into contact with acidic and basic soils, hydrolysis may be expected. No information on the stability of the test substance **CAS: ff** during the test was available. Thus, the apparent high degree of adsorption for **CAS: ff** (and thus **CAS: 126-57-8)** may also have been caused by the fact that the test substance was destroyed.
3. Although it was stated that all laboratory work undertaken was done using Good Laboratory Procedures, no signed GLP statement was included in the report.
4. The structure of the test substance as given in the report and provided by the sponsor was not correct for the CAS-number given.

Klimisch criterium 3 No information on test procedure (note 1) or stability of test substance (note 2).

2.26

Title Schedule II notification related studies for **CAS:** 126-57-8; 2. Hydrolysis; Preliminary

Date of report July 24, 1997.

GLP No.

Test substance CAS: 126-57-a; trimethylolpropane tripelargonate, purity 100%.

Test method Not indicated.

Procedure

Test system Solutions at pH 4, 7 and 9.

Procedure As the concentrations of **CAS:** 126-57-8 in buffer solutions would have been too low to be determined with acceptable accuracy, the (preliminary) hydrolysis test was performed with the structurally related **CAS:** ff.

Results

pH	Hydrolysis ± SD [%]
4	96±2
7	49±11
9	100±0

Conclusion Hydrolysis of **CAS:** ff at pH 4, 7 and 9 was respectively 96, 49 and 100%. The hydrolytic stability of **CAS:** 126-57-8 was expected to be similar.

Rev. note
1. The information available was restricted to what is included in the above summary. The actual report for the hydrolysis of CAS: ff was not available to the reviewer.
2. Although it was stated that all laboratory work undertaken was done using Good Laboratory Procedures, no signed GLP statement was included in the report.
3. In the report it is stated that the hydrolysis of **CAS: 126-57-8** and CAS: ff should be comparable:
   - the chemical structures of **CAS:** ff and **CAS:** 126-57-8 were identical near the site of hydrolysis (C-O-bond);
   - two additional methylene units on the R groups of **CAS:** 126-57-8 were not expected to have any significant effect on the reactivity of the carbonyl carbons which are involved in nucleophilic attack in the hydrolysis reaction.

Klimisch criterium 4 Secondary literature (note 1)

2.27

Title Test substance: **CAS: 11138-60-6** Physical/chemical testing for CEPA regulations; 7. Hydrolysis; preliminary

Date of report August 30, 1996.

GLP No.

Test substance CAS: 11138-60-6; multicomponent mixture.

Test method OECD 111.

Procedure

Test systems Phthalate buffer (pH 4.0), phosphate buffer (pH 7.0), borate buffer (pH 9.0), all prepared in ultrapure water. Adjustment of pH in buffers with 6N NaOH.

Procedure Solutions (0.15 % acetonitrile) of approximately 0.38 mg/L **CAS: 11138-60-6** in the various buffers were prepared. One set of solutions were placed in an incubator at 50°C and another was placed in a freezer at -20°C. After 5 days the solutions were extracted with 2 mL methyl *t*-butyl ether and 1 µL of extract was analysed by GC-FID.
Blanks (without test substance at 50°C) were included.

Results

	concentration after 5 days (mg/L)		
solution	pH 4	pH 7	pH 9
blank	0	0	0
-20°C	0.49	0.36	0.38
50°C	0.26	0.13	0.27

Conclusion Hydrolysis after 5 days at pH 4, 7 and 9 was resoectivelv 48. 65 and 27%.

Rev. note
1. Calculation of the hydrolysis was based on the assumption that frozen samples did not undergo hydrolysis, even before they were put into the freezer and upon thawing and work-up.
2. Based on the ester structure of the test substance, hydrolysis was expected at pH 4 and 9. However, it is puzzling and contrary to expectation that the largest extent of hydrolysis is found at pH 7.

Klimisch criterium 2 Hydrolysis controls (note 1), effect pH (note 2).

Appendix 3 - Ecotoxicity Data for the Aliphatic Esters

Acute Fish

GROUP A

No data available.

GROUP B

3.02

Title	**CAS: 16958-92-2:** Toxicity to the brown shrimp (Crangon *crangon*)	
Date of report	October 13, 1986.	
GLP	No.	
Test substance	CAS: 16958-92-2; purity 100%.	
Guideline	Not indicated.	
Stat. method	Stephan et *al.*, 1977	
Test system	**Species**	Brown shrimp (***Crangon*** *crangon*), mean weight 0.7 g.
	No. of fish	20/treatment.
	Concentrations	Nominal: 5600 and 10000 mg/L, untreated controls.
	Test conditions	96-h semi-static test (renewals at 24 and 48 h) under continuous agitation in cylindric glass vessels (0: 29 cm, h: 30 cm) containing 16 L seawater (salinity 35 ppt, pH 8.2), unfed; loading 0.9 g/L.
	Analysis	No analysis was performed.
	Phys. meas.	Overall ranges for pH 8.2-8.5; O_2 89-98%; temperature 15-l 6°C.
	Observations	Mortality at 24, 48, 72 and 96 h.

Results

		Nominal concentration [mg/L]		
Parameter	**Time [h]**	**0**	***5600***	**10000**
Mortality [%]	96	10	0	5

Conclusion The 96-h LC_{50} was >10000 mg/L.

Rev. note
1. No analysis was performed to confirm the nominal concentrations. Since the test substance is not soluble in the water and there is no information about the preparation of the test solution, the LC_{50}-value is not reliable.
2. During the test 0-25% organisms per treatment jumped out of the vessel, so the test vessels used were actually not appropriate for this test. Further O-l 0% organisms per treatment were eaten; this could be due to the fact that the organisms were not fed during the study.
3. *Crangon crangon* is not the species recommended by the guideline OPPTS 850.1035. The temperature used in this study is not in accordance with the guideline (15-l 6°C, OPPTS 850.1035: 25±2°C). This could be related to the species used in this test.
4. Light regime was not reported (OPPTS 850.1035: 14 h light), salinity was rather high (35 ppt, OPPTS 850.1035: 20±3 ppt).

Klimisch criterium 3 LC_{50}-value is not reliable (note 1).

3.03

Title Static 96-hour acute toxicity study of **CAS: 16958-92-2** to Sheepshead minnows

Date of report October 7, 1986.

GLP No.

Test substance CAS: 16958-92-2; purity 100%.

Guideline None.

Stat. method Binominal probability analysis (Stephan et *a/.,* 1977).

Test system

Species Sheepshead minnow *(Cyprinodon variegatus),* weight 0.3-0.4 g.

No. of fish 20/treatment.

Concentrations Nominal: 500, 1000, 2500 and 5000 mg/L, untreated control, positive control (300 mg/L diesel oil).

Test conditions 96-h static test in -40 L glass aquaria containing 30 L synthetic seawater (salinity 20±1 ppt) at 22±2°C, 16 h light, unfed. The test substance (oil) was maintained in suspension by a propeller above the system which created a vortex of 0.6-l .3 cm.

Analysis No analysis was performed.

Phys. meas. Daily, overall ranges for pH 8.1-8.2; O_2 92-106%; temperature 21-22°C, salinity 20 ppt.

Observations Mortality at 0, 24, 48, 72 and 96 h.

Results

		Nominal concentration [mg/L]					
Parameter	**Time [h]**	**0**	**500**	**1000**	**2500**	**5000**	**pos. control**
Mortality [%]	96	0	0	0	**5**	**20**	**15**

Conclusion 96-h LC_{50} >5000 mg/L.

Rev. note
1. Because the test substance is not soluble in water, it is kept in suspension by a propeller situated above the water surface. There was no information about the validity of the method used for homogenisation of the test substance in the water. The LC50 is determined using the nominal concentration, because no analyses were performed. The study reliability is lowered.
2. *Minor remark.* Food was withheld only 24 h before start of the study. (OPPTS 850.1075, 48 h). Fish that are withheld from food are more sensitive.
3. Diesel oil was used as a positive control in this study. There is no information about the effectiveness of this positive control in the system. The response is too low for a normal positive control.

Klimisch criterium 3 Exposure level fish not evident (note 1), response positive control (note 3).

3.04

Title	Acute toxicity to golden orfe
Date of report	April 19, 1994.
GLP	No.
Test substance	CAS: 122-62-3, purity not indicated.
Guideline	92/69/EEC, OECD 203.
Stat. method	Not specified.
Test system	**Species** Golden orfe (*Leuciscus idus*), length 57±2 mm.
	No. of fish 1 O/replicate, 2 replicates/treatment, 1 replicate for control.
	Concentrations Water Accommodating Fraction (WAF) at loading rate 1000 mg/L, control.
	Test conditions 96-h semi-static (renewals at 24, 48, 72 h) with dechlorinated tap water (hardness -100 mg/L $CaCO_3$); 21 °C in 20 L glass vessels, aerated; loading 0.98 g/L.
	Analysis TOC-analysis fresh medium at 0 and 72 h; old medium at 24 and 96 h.
	Phys. meas. None.
	Observations Mortality at 3, 6, 24, 48, 72 and 96 h.
Results	Analysis 1 st table below; biological results 2nd table below.

Analysis

	Concentration TOC; Concentration test substance (corrected for control) [mg/L]			
nominal rate (mg/L)	**0 h (fresh)**	**24 h (old)**	**72 h (fresh)**	**96 h (old)**
0 (control)	2.4; 0	2.3; 0	1.9; 0	2.8; 0
1000 (repl. 1)	2.2; -	3.6; 1.8	0.84; -	1.9; -
1000 (repl. 2)	2.0; -	3.2; 1.2	1.8; -	1.7; -

Biological results

		Nominal concentration [mg/L]	
Parameter	**Time [h]**	**0**	**1000**
Mortality [%]	96	None	

Conclusion	Solubility of test substance is very low; no conclusion about toxicity test substance (note 1).
Rev. **note**	1. WAF was prepared by 24 h stirring followed by 1 h equilibrating. 2. The analytical results show very low concentrations of the test substance in the test solutions. This could partly be due to the inhomogeneity of the solution, but mostly to the very low solubility of the test substance in the water. Probably the water system is not sensitive for the toxicity of the test substance due to its low solubility, but no reliable LC50 value originates from this study. 3. No information was available about the light regime, feeding of the fish, pH and oxygen concentration in the report.
Klimisch criterium	3 No reliable LC50-value (note 2), limited information (note 3).

3.05

Title	Fischtest, akute Toxizität.
Date of report	November 8, 1993.
GLP	No.
Test substance	CAS: 28472-97-1, purity not indicated.
Guideline	OECD 203; 92/69/EWG (1992).
Stat. method	None.
Test system	**Species** Golden *orfe (Leuciscus idus melanotus* L.), age 4 weeks.
	No. of fish 1 O/treatment.
	Concentrations Nominal: 10000 mg/L, untreated controls.
	Test conditions 96-h static test with drinking water (hardness 255±51 mg/L $CaCO_3$); 20±1 °C in 8.4 L glass vessels, aerated; unfed.
	Analysis Not performed.
	Phys. meas. Daily in all treatments: overall ranges for pH 8.3-8.6; O_2 80-l 00%.
	Observations Mortality at 24, 48, 72 and 96 h.

Results

Parameter	Time [h]	Nominal concentration [mg/L]	
		0	10000
Mortality [%]	96	None	

Conclusion The 96-h LC_{50} cannot be determined (note 2).

Rev. note
1. Incomplete description: Only the age of the fish and the volume of the test vessels was reported. It can not be checked if the fish have the recommended length (60±20 mm) and that the biological loading during the test was acceptable (<1 g/L). Further the photoperiod during the test was not reported and no temperature measurements were carried out.
2. Probably a WAF is used in this study. WAF is the maximum soluble concentration of the nominal test concentrations. Since no analytical measurements were performed, no reliable LC_{50} value can be given.

Klimisch criterium 3 Incomplete description (note 1), LC_{50} cannot be determined (note 2).

3.06

Title 96-hour acute toxicity study in carp with **CAS:** 103-24-2 for W.G.K. (static)

Date of report June 29, 1998.

GLP **Yes.**

Test substance CAS: 103-24-2; purity not indicated.

Guideline OECD 203, EEC L383 92/69 C 1 (1992).

Stat. method None.

Test system

Species Carp (*Cyprinus carpio*), mean length 20±1 mm.

No. of fish 3/treatment for 1, 10, 100 and 1000 mg/L; 7/treatment for 10000 mg/L and control.

Concentrations Water Accommodated Fractions (WAF, see note 1) prepared at nominal 1, 10, 100, 1000 and 10000 mg/L, untreated controls.

Test conditions 96-h static test with ISO-medium (pH 8.1, hardness 250 mg/L $CaCO_3$) in 3-4 L glass vessels containing 152.5 L medium, aerated; 16 h light; unfed; loading 50.5 g/L.

Analysis No analysis was performed.

Phys. meas. Daily in control vessel: overall ranges for temperature 20-21°C; pH 7.3-8.1 (also in 10000 mg/L); O_2 74-100% (in all vessels), except in the 10000 mg/L vessel at day 2); O_2 36%.

Observations Mortality/symptoms at 2, 24, 48, 72 and 96 h.

Results At concentrations ≥10 mg/L a film of test substance appeared at the surface.

Parameter	Time [h]	Nominal concentration [mg/L]					
		0	1	10	100	1000	10000
Mortality [%]	96	14	0	0	0	0	0
Symptoms*	O-96				+	+	+

* Symptoms included hypoactive swimming, haemorrhage of the tail and/or gills, loss of equilibrium, immobile and/or swimming at the surface and/or at the bottom

Conclusion The 96-h LC_{50} could not be determined (note 1).

Rev. note
1. WAF is the maximum soluble concentration of the nominal test concentrations after 48 hours of stirring. Only the water phase was used in the definitive test solutions. Further the WAF did not stay in solution for concentrations ≥10 mg/L. Since no analytical measurements were performed, no reliable LC_{50} value can be given.
2. At day 2 the oxygen concentration dropped to 36% of the saturation level. Since no mortality occurred, it can be concluded that there has been no effect on the outcome of the study.

Klimisch criterium 2 LC_{50} cannot be determined (note 1)

3.07

Title	Fischtest, akute Toxizitat.	
Date of report	November 8, 1993.	
GLP	No.	
Test substance	CAS: 28472-97-1, purity not indicated.	
Guideline	OECD 203; 92/69/EWG (1992).	
Stat. method	None.	
Test system	**Species**	Golden orfe (*Leuciscus idus melanotus* L.), age 4 weeks.
	No. of fish	1 O/treatment.
	Concentrations	Nominal: 10000 mg/L, untreated controls,
	Test conditions	96-h static test with drinking water (hardness 255±51 mg/L $CaCO_3$); 20±1 °C in 8.4 L glass vessels, aerated: unfed.
	Analysis	Not performed.
	Phys. meas.	Daily in all treatments: overall ranges for pH 8.3-8.4; O_2 76-98%.
	Observations	Mortality at 24, 48, 72 and 96 h.

Results

		Nominal concentration [mg/L]	
Parameter	**Time [h]**	**0**	**10000**
Mortality [%]	96	None	

Conclusion The 96-h LC_{50} cannot be determined (note 2).

Rev. note

1. Incomplete description: Only the age of the fish and the volume of the test vessels was reported. It can not be checked if the fish have the recommended length (60±20 mm) and that the biological loading during the test was acceptable (<1 g/L). Further the photoperiod during the test was not reported and no temperature measurements were carried out.
2. Probably a WAF is used in this study. WAF is the maximum soluble concentration of the nominal test concentrations. Since no analytical measurements were performed, no reliable LC_{50} value can be given

Klimisch criterium 3 Incomplete description (note I), LC_{50} cannot be determined (note 2).

GROUP C

3.08

Title	Rainbow trout acute toxicity tests	
Date of report	September 17, 1993.	
GLP	No.	
Test substance	CAS: 67989-24-6 en 70024-57-6.	
Guideline	OECD 203 (1981).	
Stat. method	Trimmed Spearman Karber analysis.	
Test system	**Species**	Rainbow trout (*Oncorhynchus mykiss*), length -50 mm.
	No. of fish	1 O/vessel, 2 vessels/treatment.
	Concentrations	Nominal: 40.5, 135, 450, 1500 and 5000 µL/L, untreated controls.
	Test conditions	96-h static test with water (hardness 66-68 mg/L $CaCO_3$); 15±1 °C in 20 L glass vessels containing 6 L water; 16 h light; unfed; aerated. The test substance (oil) was emulsified using a blender.
	Analysis	No analysis was performed.
	Phys. meas.	Daily in all vessels: overall ranges for pH 7.1-7.5; O_2 60-83%; temperature 14-16°C.
	Observations	Mortality/symptoms at 24, 48, 72 and 96 h.

Results Some surface "pooling" was observed (note 2).

Parameter	Time [h]	Nominal concentration [µL/L]					
		0	40.5	135	450	1500	5000
Mortality [%]	96	0	0	0	5	20	100

Conclusion The 96-h LC50 calculated by the author was 2027 µL/L (95% Cl: 1586-2590 µL/L).

Rev. note
1. The biological loading was not specified in the report. It is not excluded that the biological loading exceeded 1 g fish/L, since a mean weight of 0.6 gram for fish with a length of -50 mm seems rather low. Fish can get stressed because of this overloading, so in a worst case approach it is acceptable.
2. Because the test substance is not soluble in water, a suspension of the test substance in water is used. The emulsions were reported to be reasonable stable, but surface pooling was observed. The fish can be exposed to lower concentrations, the study reliability is lowered.

Klimisch criterium 2 Exposure level fish not evident (note 2), possible overloading (note 1).

3.09

Title Acute toxicity in golden orfe (Leuciscus *idus*) according to DIN 38412, part 15

Date of report September 10, 1991.

GLP **Yes.**

Test substance CAS 70729-68-g (tetraethylene glycol diheptanoate); purity 94.5%, 2% monoesters

Guideline DIN 38412, part 15.

Stat. method Not applicable according to the author.

Test system

Species Golden orfe *(Leuciscus idus)*, mean length 53 mm.

No. of fish 5/vessel; 2 vessels/treatment.

Concentrations Nominal dispersions of 18, 32, 56, 100, 180, 320, 560 and 1000 mg/L, untreated controls.

Test conditions 48-h static test in 12 L vessels containing 10 L of dechlorinated tap water (hardness 250 mg $CaCO_3$/L) at 18-22°C, aerated, 16 h light, unfed, loading 0.74 g fish/L.

Analysis No analyses were performed.

Phys. meas. Daily, overall ranges for pH 7.9-8.2; O_2 60-l 00%; temperature 17-20%.

Observations Mortality/symptoms at 2-4, 24 and 48 h.

Results

Parameter	Time [h]	Nominal concentration [mg/L]									DR
		0	18	32	56	100	180	320	560	1000	
Mortality [%]	48	0	0	0	0	0	0	0	20	90	X
Oily drops on the surface	0-48					+	+	+	+(A)	+(A)	X

(A) the dispersion appeared clearer

Conclusion 48-h LC_{50} 720 mg/L (graphical determination).

Rev. note
1. Test concentrations were all above the water solubility of the test compound (EPIWIN 0.34 mg/L). There is no information on the homogeneity of the test "solutions" and no analyses were performed to confirm the nominal test concentrations. The mortality found in this study may be not related to toxic effects, but to physical effects (sorption of oily substance to the fish). The test reliability was lowered because of this.
2. The test duration was only 48 hours. It cannot be excluded that the LC_{50} after 96 hours was significantly different from that after 24 hours.
3. *Minor remark. Leuciscus idus* was not recommended by OECD 203. However in the EG guidelines *Leuciscus idus* is included as a recommend fish species. The test temperature was rather low (17-20°C, EG 20-24°C).

Klimisch criterium 3 No analyses, physical effects (note 1).

3.10

Title 24-hour LC50 to zebra fish
Date **of report** June 18, 1981.
GLP No.
Test substance CAS: 70729-68-9, purity: 88%, 6% triethylene glycol di-n-heptanoate, 4% mixed ester of tetraethylene glycol with n-heptanoic and 2 methylhexanoic acids, 2% other mixed esters.
Guideline Not indicated.
Stat. method Not indicated.
Test system
- **Species** Zebra fish (*Brachydanio rerio*), mean length 25 mm.
- **No. of fish** 10/treatment.
- **Concentrations** Nominal: 0.56, 0.75, 1.0, 2.4, 3.2, 4.2, 5.6, 7.5 and 10 g/L, untreated controls.
- **Test conditions** 24-h static test in glass vessels containing 15 L of laboratory supply water (hardness 90 mg $CaCO_3$/L) at 20°C, not aerated, 16 h light, unfed, loading 0.2 g fish/L.
- **Analysis** No analyses were performed.
- **Phys. meas.** At 0 and 24 h in control, 0.56, 4.2 and 10 g/L: ranges for pH 7.0-7.3; O_2 76-97%.
- **Observations** Mortality/symptoms at 24 h.

Results

Parameter	Time [h]	Nominal concentration [g/L] 0	0.56	0.75	1.0	2.4	3.2	4.2	5.6	7.5	10	DR
Mortality [%]	*24*	0	0	0	0	10	20	0	90	100	100	x
Symptoms[A]	*0-24*					+	+		+	+	+	

(A) Symptoms included darkening of the fish, loss of equilibrium and/or erratic swimming:

Conclusion 24-h LC_{50} calculated by the reviewer using 20% trimmed SPK was 4.8 g/L (95% CI 4.6-5.1 g/L) ⇔ 4.3 g a.i./L (95% CI 4.1-4.5 g a.i./L).

Rev. **note**
4. Test concentrations were all above the water solubility of the test compound (EPIWIN 0.34 mg/L). There is no information on the homogeneity of the test "solutions" and no analyses were performed to confirm the nominal test concentrations. The mortality found in this study may be not related to toxic effects, but to physical effects (sorption of oily substance to the fish). The test reliability was lowered because of this.
5. The test duration was only 24 hours. It cannot be excluded that the LC_{50} after 96 hours was significantly different from that after 24 hours.
6. *Minor remark.* The test temperature was rather low (20°C, OECD 203 21-25°C).

Klimisch criterium 3 No analyses, physical effects (note 1).

GROUP D

3.11

Title **CAS: 1336-39-2:** Acute toxicity to rainbow trout *(Salmo gairdneri)*
Date of report May 4, 1988.
GLP No.
Test substance CAS: 1338-39-2., purity not indicated
Guideline Not indicated.
Stat. method Not indicated.
Test system
- **Species** Rainbow trout (*Salmo gairdneri*), mean weight 2.67 g.
- **No. of fish** 10/treatment.
- **Concentrations** Nominal: 0, 10, 18, 32, 56 and 100 mg/L.
- **Test conditions** 96-h static test; aerated, 15±1 °C.
- **Observations** Mortality at 24, 48, 72 and 96 h.

Results

Parameter	Time [h]	Nominal concentration [mg/L]					
		0	10	18	32	56	100
Mortality [%]	96	0	0	0	0	0	100

Conclusion The 96-h LC_{50} calculated by the author was 75 mg/L.
Rev. note Only a summary of a study was available. The information is limited to what is included above. No conclusion can be drawn about the validity of the test, because of the limited information available.
Klimisch criterium 3 Incomplete report.

3.12
Title **CAS: 1338-43-8:** Acute toxicity to rainbow trout (*Salmo gairdneri*)
Date of report May 4, 1988.
GLP No.
Test substance CAS: 1338-43-8, purity not indicated.
Guideline Not indicated.
Stat. method Not applicable.
Test system
Species Rainbow trout (*Salmo gairdneri*), mean weight 0.91 g.
No. of fish 10/treatment.
Concentrations Nominal: 0 and 1000 mg/L.
Test conditions Limit test, 96-h static; aerated, 15±1 °C.
Observations Mortality at 24, 48, 72 and 96 h.
Test substance was not in solution.

Results

Parameter	Time [h]	Nominal concentration [mg/L]	
		0	1000
Mortality [%]	96	None	

Conclusion The 96-h LC_{50} based on nominal concentrations was >1 000 mg/L.
Rev. note Only a summary of a study was available. The information is limited to what is included above. No conclusion can be drawn about the validity of the test, because of the limited information available.
Klimisch criterium 4 Incomplete report.

GROUP E

3.13
Title Static 96-hour acute toxicity study of **CAS:** 67762-53-2; 67762-52-l to Rainbow trout
Date of report January 2, 1993.
GLP No.
Test substance CAS: 67762-53-2: 88%; CAS: 67762-52-l : 12%.
Guideline EC, L 251/146-154 C 1 (1984).
Stat. method Binominal probability analysis (Stephan et al.)
Test system
Species Rainbow trout (*Oncorhynchus mykiss*), mean length 28-31 mm.
No. of fish 20/treatment.
Concentrations Nominal: 97, 517, 1002, 2005 and 5012 mg/L, untreated controls.
Test conditions 96-h static test with MTC well water (hardness 211 mg/L $CaCO_3$); 12±2°C in -40 L glass vessels containing 30 L water; 16 h light; unfed; loading 0.2 g/L. The test substance (oil) was maintained in suspension by a propeller above the system which created a vortex of 0.6-l .3 cm.
Analysis No analysis was performed.
Phys. meas. Daily in all treatments: pH 8.2; O_2 84-94%; temperature 1 l-l 2°C.
Observations Mortality at 24, 48, 72 and 96 h.

Results Due to cloudiness in the three highest doses groups, no observations could been made during the study.

Parameter	Time [h]	Nominal concentration [mg/L] 0	97	517	1002	2005	5012
Mortality [%]	96	None					

Conclusion The 96-h LC_{50} was >5012 mg/L.

Rev. note
1. The fish were rather small (30 mm, EC L 383 A: 60±20 mm). Since small fish are more sensitive, this is acceptable in a worst case approach.
2. Because the test substance is not soluble in water, it is kept in suspension by a propeller situated above the water surface. There was no information about the validity of the method used for homogenisation of the test substance in the water. There were also no analyses performed to confirm the nominal concentration of the test substance in the water. The study reliability is lowered.
3. *Minor* remark The temperature during the study is somewhat lower than required (11-12°C, EC L 383 A: 12-17°C; OECD 203: 13-17°C).

Klimisch criterium 2 Exposure level fish not evident (note 2), small fish (note 1).

3.14

Title A static 96-hour acute toxicity study of the water soluble fraction of **CAS: 11138-60-6** to mysid shrimp (*Mysidopsis bahia*)

Date of report July 1, 1991.

GLP No.

Test substance CAS: 11138-60-6; purity 100%.

Guideline Not indicated.

Stat. method Binominal probability analysis (Stephan et *al.*, 1977).

Test system

Species Mysid shrimp (*Mysidopsis bahia*), 3-6 days old.

No. of fish 1 O/dish, 2 dishes/treatment.

Concentrations Water soluble fraction (WSF) of 95, 568, 1014, 1987 and 5014 mg/L, untreated controls.

Test conditions 96-h static test in 1 L cylindrical Pyrex crystallising dishes (covered) containing 400 mL synthetic seawater (salinity 20±2 ppt) at 20±2°C, 16 h light, fed daily.

Analysis No analysis was performed.

Phys. meas. Daily, overall ranges for pH 8.4; O_2 80-97%; temperature 22°C, salinity 20-24 ppt.

Observations Mortality at 0, 24, 48, 72 and 96 h.

Results

Parameter	Time [h]	Nominal concentration [mg/L] 0	95	568	1014	1987	5014
Mortality [%]	96	0	0	5	5	0	5

Conclusion No reliable 96-h LC_{50} can be deduced from this study.

Rev. note
1. WSF is the water soluble fraction prepared by stirring for 20 hours followed by 4 hours of settling. So the actual concentration is not equal to the nominal. Since there were also no analytical measurements, the actual concentrations used in the test are not available. Probably the water system is not sensitive for the toxicity of the test substance due to its low solubility. No reliable LC50 value originates from this study.
2. Temperature and light regime were not in accordance with the guideline (22°C and 16 h light, OPPTS 850.1035 25±2°C and 14 h light). Both can have an effect on the activity of the organism:
   - Lower temperature ⇒ lower activity ⇒ less sensitive organisms;
   - More light ⇒ higher activity ⇒ more sensitive organisms.

Klimisch criterium 3 Concentration not clear (note 1).

3.15

Title	Static 96-hour acute toxicity study of **CAS: 11138-60-6** to Rainbow trout	
Date of report	November 26, 1996.	
GLP	Yes.	
Test substance	CAS: 11138-60-6; purity 100%.	
Guideline	**OECD 203; EC L 383A/163-171 C 1 (1992).**	
Stat. method	Binominal probability analysis (Stephan et *al., 1978)*	
Test system	**Species**	Rainbow trout (*Oncorhynchus mykiss*), mean length 30-32 mm.
	No. of fish	20/treatment.
	Concentrations	Nominal: 65, 129, 259, 517 and 1035 mg/L, untreated controls.
	Test conditions	96-h static test (hardness 203 mg/L $CaCO_3$); 12±1 °C in -40 L glass vessels containing 30 L well water; 16 h light; unfed; loading 0.2-0.3 g/L. The test substance (oil) was maintained in suspension by a propeller above the system which created a vortex of 0.6-l .3 cm.
	Analysis	At 0 and 96 h from control, 65, 259 and 1035 mg/L by extraction/GC-FID.
	Phys. meas.	Daily in all treatments: overall ranges for pH 7.8-8.2; O_2 77-90%; temperature 1 l-1 3°C.
	Observations	Mortality/symptoms at 24, 48, 72 and 96 h.
Results	**Analysis**	LOD 0.12 mg/L; measured concentrations for 65, 259 and 1035 mg/L nominal ranged from respectively 167, 37 and 214% at start to 308, 81 and 13% at the end of the test (n=1).

		Nominal concentration [mg/L]					
Parameter	**Time [h]**	**0**	**65**	**129**	**259**	**517**	**1035**
Mortality [%]	96	0	0	0	0	0	5

Conclusion The 96-h LC_{50} was >1035 mg/L.

Rev. note

1. The fish were rather small (30 mm, EC L 383 A: 60±20 mm). Since small fish are more sensitive, this is acceptable in a worst case approach.
2. Because the test substance is not soluble in water, it is kept in suspension by a propeller situated above the water surface. There was no information about the validity of the method used for homogenisation of the test substance in the water. Further only single analyses were performed to determine the actual concentration of the test substance during the test. The nominal concentration is not confirmed by this analysis. The LC50 is determined using the nominal concentration, because no reliable estimate of the actual concentration can be made using the results of the analysis. The study reliability is lowered.
3. *Minor remark* The temperature during the study is somewhat lower than required (11-13°C, EC L 383 A: **12-17°C).**

Klimisch criterium 2 Exposure level fish not evident (note 2), small fish (note 1).

3.16

Title	A static 96-hour acute toxicity study of **CAS: 11138-60-6** to Sheepshead minnow	
Date of report	June 21, 1991.	
GLP	No.	
Test substance	**CAS:** 11138-60-6; purity 100%.	
Guideline	EEC L. **251/146-l 54; Cl.**	
Stat. method	Binominal probability analysis (Stephan et *al., 1977).*	
Test system	**Species**	Sheepshead minnow (*Cyprinodon variesatus*), weight 0.08-0.1 g.
	No. of fish	20/treatment.
	Concentrations	Nominal: 101, 504, 1009, 2018 and 5045 mg/L. untreated controls.
	Test conditions	96-h static test in -40 L glass aquaria containing 30 L synthetic seawater (salinity 20±2 ppt) at 20±2°C, 16 h light, unfed. The test substance (oil) was maintained in suspension by a propeller above the system which created a vortex of 0.6-l .3 cm.
	Analysis	No analysis was performed.
	Phys. meas.	Daily, overall ranges for pH 8.1-8.4; O_2 81-101%; temperature 21-22°C, salinity 20-21 ppt.
	Observations	Mortality at 96 h (note 1).

Results

Parameter	Time [h]	Nominal concentration [mg/L]					
		0	101	504	1009	2018	5045
Mortality [%]	96	0	0	0	5	0	5

Conclusion 96-h LC_{50} >5045 mg/L.

Rev. note
1. *Minor remarks.* Due to cloudiness of the test solutions mortality counts could only be performed at the end of the test for the three highest concentrations. Food was withheld only 24 h before start of the study. (OPPTS 850.1075, 48 h). Fish that are withheld from food are more sensitive.
2. Because the test substance is not soluble in water, it is kept in suspension by a propeller situated above the water surface. There was no information about the validity of the method used for homogenisation of the test substance in the water. The LC_{50} is determined using the nominal concentration, because no analysis were performed. The study reliability is lowered.

Klimisch criterium 3 Exposure level fish not evident (note 2).

3.17

Title Acute toxicity study with *Cyprinus carpio* exposed to CAS: 126-57-8

Date of report August 24, 1988.

GLP Yes.

Test substance CAS:126-57-8, purity -100%.

Guideline Niemitz, LTwS, Nrl 0, 1979.

Stat. method None.

Test system

Species Carp (*Cyprinus carpio),* length 20-40 mm.

No. of fish 1 O/treatment

Concentrations Nominal 1000 mg/L, untreated control.

Test conditions 48-h static test with tap water (pH 8.2, hardness 199 mg/L $CaCO_3$) in 10 L glass vessels containing 5 L medium, aerated; unfed. Test substance was a suspension.

Analysis No analysis was performed.

Phys. meas. At 0 and 48 h in control and highest concentration: overall ranges for temperature 20-22°C; pH 8.0-8.3; O_2 83-94%.

Observations Mortality/symptoms at 2-5, 24 and 48 h.

Results

Parameter	Time [h]	Nominal concentration [mg/L]	
		0	1000
Mortality [%]	96	None	

Conclusion The 48-h LC_{50} was >1000 mg/L.

Rev. note The information in the report was essentially confined to what is included in the above summary. No analyses were performed to confirm the nominal concentration and the only information about the homogeneity of the solution was the description of the test medium as a suspension of macroscopic droplets of test substance. The lower limit of the LC50 value is probably not accurate. The study reliability is lowered.

Klimisch criterium 3 LC50 not accurate

Acute Daphnia

GROUP A

No data available.

GROUP B

3.18

Title	Acute immobilisation test of *Daphnia magna* (EU guideline 67/548/EEC)	
Date of report	October 4, 1997.	
GLP	No.	
Test substance	CAS: 16958-92-2; purity not indicated.	
Test method	OECD 202, 67/548/EEC, DIN 38412.	
Stat. method	None.	
Test system	**Species**	*Daphnia magna,* <24 h old.
	No. of daphnids	Not specified.
	Concentrations	Nominal concentrations of 0.6, 0.8, 1.1, 1.6, 2.3, 3.3, 4.6, 6.5, 9.2 and 13 g/L (10 % emulsifier **CAS: pp),** untreated controls, emulsifier controls (1.3 g **CAS: rr),** positive control (Potassium dichromate).
	Test conditions	24 h static test at 20±1 °C in reconstituted water, 16 h light, unfed, O_2 >60%.
	Analyses	None.
	Phys. meas.	Not specified.
	Observations	Immobility at 24 h.
Results	**Positive control**	EC50 1.6 mg/L

Parameter	Time[h]	Nominal concentration [g/L]										
		0	0.6	0.6	1.1	1.6	2.3	3.3	4.6	6.5	9.2	13
Immobility [%]	24	0	lo	lo	lo	1 1 5	1 3 0	1 4	5 50	60	65	80

Conclusions 24-h EC_{50} graphically determined by the author was 4.8 g/L.

Rev. note

1. The information was essentially confined to what is included in the above summary. No information on pH and number of organisms used was not defined in the report.
2. The composition and purity of the test substance was not known and no analyses were performed to estimate a reliable concentration of the test substance. The EC50 value can be overestimated because of this. The study reliability is lowered.
3. According to OECD 202 the concentration of emulsifiers should not exceed 0.1 g/L. In the current test, the concentration of emulsifier is >0.1 g/L at nominal concentrations 1 .1-1 3 g/L). Since the emulsifier controls were reported to be not toxic against *Daphnia* in the used concentrations, this is acceptable.

Klimisch criterium 3 Tested concentrations not reliable (note 2), study duration too short (24 h).

3.19

Title	Acute toxicity to *Daphnia magna*	
Date of report	March 25, 1994.	
GLP	No.	
Test substance	CAS 122-62-3; purity not indicated.	
Test method	OECD 202 (1964).	
Stat. method	Not specified.	
Test system	**Species**	*Daphnia magna.*
	No. of daphnids	lo/replicate, 4 replicates/treatment, 2 replicates/control.
	Concentrations	Water Accommodating Fraction (WAF) at loading rate 1000 mg/L, control.
	Test conditions	Limit test: 48 h-static with reconstituted water; 21°C in 200 mL exposure vessels, no aeration. Preparation WAF by 24 h stirring followed by 1 h equilibrating
	Analyses	At 0 and 48 h from control and 100 mg/L WAF by TOC analysis.
	Phys. meas.	None.
	Observations	Immobility at 24 and 48 h.

Results For analytical results see 1st table below. Biological data are shown in the 2nd table.

Analytical results

	Concentration TOC [mg/L]		Conc. TS (corrected for control) [mg/L]	
nominal rate (mg/L)	**0 h**	**48 h**	**0 h**	**48 h**
0 (control)	1.6	2.2	0	0
1000 (repl. 1)	2.1	1.5	0.72	0.94
1000 (repl. 2)	1.6	1.2	0.045	1.3

Biological results

		Nominal concentration [mg/L]	
Parameter	**Time [h]**	**0**	**1000**
Immobility [%]	48	None	

Conclusion Solubility of test substance is very low; no conclusion about toxicity test substance (note 1).

Rev. note
1. The analytical results show very low concentrations of the test substance in the test solutions. This could partly be due to the inhomogeneity of the solution, but mostly to the very low solubility of the test substance in the water. Probably the water system is not sensitive for the toxicity of the test substance due to its low solubility, but no reliable LC50 value originates from this study.
2. No information was available about the light regime, feeding and age of the *Daphnia,* pH and oxygen concentration in the report.

Klimisch criterium 3 No reliable LC50-value (note 1), limited information (note 2).

GROUP C

3.20

Title 24-hour LC50 to *Daphnia magna*

Date of report June 18, 1981.

GLP No.

Test substance CAS: 70729-68-9, purity: 88%, 6% triethylene glycol di-n-heptanoate, 4% mixed ester of tetraethylene glycol with n-heptanoic and 2 methylhexanoic acids, 2% other mixed esters.

Test method Not indicated.

Stat. method Probit analysis (Finney, 1971)

Test system
- **Species** *Daphnia magna,* <24 h old.
- **No. of daphnids** 1 O/replicate, 2 replicates/treatment.
- **Concentrations** Nominal: 0.56, 0.75, 1.0, 2.4, 3.2, 4.2, 5.6, 7.5 and 10 g/L, untreated controls.
- **Test conditions** 24 h-static test at 20°C in 250 mL glass beakers containing 200 mL laboratory test water of hardness 104 mg/L ($CaCO_3$), 16 h light, unfed.
- **Analyses** No analyses were performed.
- **Phys. meas.** At 0 and 24 h in control, 0.56, 4.2 and 10 g/L: ranges for pH 6.6-7.5; O_2 89-91% (t=O).
- **Observations** Immobility/symptoms at 24 h.

Results

		Nominal concentration [g/L]									
Parameter	**Time [h]**	**0**	0.56	0.75	**1.0**	**2.4**	**3.2**	**4.2**	**5.6**	**7.5**	**10**
Immobility [%]	24	0	5	0	15	15	55	70	35	90	100
Symptoms	O-24	Not reported									
Dissolved oxygen [%]	24	80	12					3			3

Conclusions 24-h LC50 3.8 g/L (95% Cl 1.4-6.3 g/L).

Rev. note
1. Test concentrations were all above the water solubility of the test compound (EPIWIN 0.34 mg/L). There is no information on the homogeneity of the test "solutions" and no analyses were performed to confirm the nominal test concentrations. The test reliability was lowered because of this.
2. The oxygen concentration fell below 60% of saturation during the study. This will most probably affect the study outcome, but is acceptable in a worst case approach.

Klimisch criterium 3 No reliable LC50 value (note 1)

GROUP D

No data available.

GROUP E

3.21

Title		Static renewal three-brood chronic survival and reproduction study of the water-accommodated fractions (WAFs) of **CAS: 11138-60-6** to *Daphnia* magna
Date of report		November 26, 1996.
GLP		Yes.
Test substance		CAS: 11138-60-6; purity 100%.
Test method		OECD 202, EEC Directive 92/69/EEC L383 A.
Stat. method		Binomial orobability analysis (Stephan et *al.*, 1978)
Test system	**Species**	*Daphnia magna,* <24 h old.
	No. of daphids	l/beaker, 10 beakers/treatment.
	Concentrations	Water Accommodated Fractions (WAF, see note 1) prepared at 24, 97, 242, 1018 and 2570 mg/L, untreated controls.
	Test conditions	Semi-static without aeration for 15 days with renewal every 2 days; at 20±1 °C in 50 mL polystyrene containers, containing 40 mL of MTC well water (hardness 202 mg $CaCO_3$/L); 16 h light; feeding daily with a mixture of algae and/or dried yeast.
	Analysis	For 0, 24, 242 and 2570 mg/L from fresh and old media on day 14 (method: extraction followed by GC/FID).
	Phys. meas.	At renewals in fresh and old solutions: overall ranges for pH 7.8-8.4; O_2 86-l 00%, temperature 19-21 °C.
	Observations	Immobilisation parents daily; no. of larvae.
Results	**Analysis**	Test substance was not detectable in any of the samples (<0.03 mg/L)
	Biological	Reproduction in control started at day 9, further see table below.

Biological results

		Nominal concentration [mg/L]					
Parameter	**Time [d]**	**0**	**24**	**97**	**242**	**1018**	**2570**
Mortality parents [%]	15	0	0	20	0	0	0
No. of offspring/surviving adult	9-15	No treatment related effects					

Conclusion	Solubility of test substance is very low; no conclusion about toxicity of test substance is drawn (note 2).
Rev. **note**	1. WAF is the maximum soluble concentration of the nominal test concentrations after 20 hours of stirring and 4 hours of equilibrating. Only the water phase was used in the definitive test solutions. 2. The test substance was not detected during the study, so the measured concentration was <0.03 mg/L. This could partly be due to the inhomogeneity of the solution, but mostly to the very low solubility of the test substance in the water. Probably the water system is not sensitive for the toxicity of the test substance due to its low solubility, but no reliable NOEC value originates from this study. 3. The study is in accordance with OECD 211 (adapted version of OECD 202), but only a few parameters were included in the study
Klimisch criterium	3 Concentration not confirmed (note 2)

3.22

Title	Static 48-hour acute toxicity study of the Water-Accommodated Fraction (WAF) of **CAS: 11138-60-6** to *Daphnia magna*	
Date of report	November 26, 1996.	
GLP	Yes.	
Test substance	CAS: 11138-60-6; purity 100%.	
Test method	OECD 202, EEC Directive 92/69/EEC L383 A.	
Stat. method	Binomial probability analysis (Stephan et *a/.,* 1978)	
Test system	**Species**	*Daphnia magna,* <24 h old.
	No. of daphnids	1 O/replicate, 2 replicates/treatment.
	Concentrations	Water Accommodated Fractions (WAF, see note 1) prepared at 24, 97, 242, 1018 and 2570 mg/L, untreated controls.
	Test conditions	48 h-static test at 20±1 °C in 250 mL glass beakers containing 100 mL MTC well water of hardness 203 mg/l ($CaCO_3$), 16 h light, unfed.
	Analyses	At 0 and 48 h for WAF concentrations of 0, 24, 242 and 2570 mg/L (method: extraction followed by GC/FID).
	Phys. meas.	At 0 and 48 h for all concentrations; overall ranges for pH 8.1-8.5; O_2 89-95% and temperature 20°C.
	Observations	Immobility/symptoms at 0, 24 and 48 h.
Results	**Analyses**	For analytical results see 1st table below. LOD was 0.12 mg/L.
	Biological	Biological data are shown in the 2nd table.

Analytical results

Nominal conc. [mg/L]	Measured concentration [mg/L]	
	0 h	48 h
0	nd	nd
24	0.41	nd
242	0.13	nd
2570	0.21	19

Biological results

		Nominal concentration [mg/L]					
Parameter	**Time [h]**	**0**	**24**	**97**	**242**	**1018**	**2570**
Immobility [%]	48	5	0	0	0	0	0
Symptoms	0-48	None					

Conclusions Solubility of test substance is very low; no conclusion about toxicity test substance (note 2).

Rev. **note**

1. WAF is the maximum soluble concentration of the nominal test concentrations after 20 hours of stirring and 4 hours of equilibrating. Only the water phase was used in the definitive test solutions.
2. The analytical results show very low concentrations of the test substance in the test solutions. This could partly be due to the inhomogeneity of the solution, but mostly to the very low solubility of the test substance in the water. Probably the water system is not sensitive for the toxicity of the test substance due to its low solubility, but no reliable LC50 value originates from this study.

Klimisch criterium 3 No reliable LC50 value (note 2)

3.23

Title	The acute toxicity of **CAS: 126-57-8** to *Daphnia magna*	
Date of report	February 23, 1996.	
GLP	Yes.	
Test substance	CAS: 126-57-8; purity 100%.	
Test method	OECD 202. EEC Directive 92/69/EEC L383 A.	
Stat. method	None.	
Test system	**Species**	*Daphnia magna,* probably <24 h old.
	No. of daphnids	lo/replicate, 2 replicates/treatment.
	Concentrations	Nominal dispersions of 1 .0, 2.4, 5.6, 13 and 32 mg/L, untreated controls.
	Test conditions	Static at 18-20°C in 100 mL glass dishes (covered with mesh), placed in 2 L dishes containing 2000 mL **CAS:** tt medium of hardness -240 mg/l ($CaCO_3$), 16 h light, unfed.
	Analyses	At 0, 24 and 48 h for all concentrations by extraction/ concentration/GC-FID. Quantification by using an internal standard.
	Phys. meas.	At 0 and 48 h for all concentrations: overall ranges for pH 7.3-7.6; O_2 79-86% and temperature 18-20°C.
	Observations	Immobility at 24 and 48 h.
Results	**Analyses**	For analytical results see 1 st table below.
	Biological	Biological data are shown in the 2nd table.

Analytical results

Nominal conc. [mg/L]	Measured concentration [% of nominal]			Mean measured conc. [% of nominal]
	0 h	24 h	48 h	
0.0	0.1 mg/L	0.1 mg/L	0.1 mg/L	0.07 mg/L
1.0	60	40	30	43
2.4	50	33	25	36
5.6	39	30	29	33
13	42	27	18	29
32	36	28	23	29

Biological results

Parameter	Time [h]	Mean measured concentration [mg/L]					
		0.07	0.4	0.9	1.8	3.8	9.3
Immobility [%]	48	5	0	0	6	0	15

Conclusions	48-h EC_{50} >9.3 mg/L.
Rev. note	1. No validation results of the analytical method were included in the report. 2. Daphnia trapped at the air/water interface, were not counted as immobile organisms, because it is not a test substance related effect. There were enough Daphnia left for a valid conclusion of the test.
Klimisch criterium	1

Algae

GROUP A

No data available.

GROUP B

3.24

Title	Growth inhibition test of *Scenedesmus subspicatus*	
Date of report	October 6, 1997.	
GLP	No.	
Test substance	CAS: 16958-92-2, purity not indicated.	
Guideline	ISO 8692.	
Stat. method	Fischer's exact test and binomial probability analysis.	
Test system	**Species**	Green algae *(Scenedesmus subspicatus)*.
	Initial cell conc.	1 x 1 0^4 cells/ml.
	No. of replicates	2 per treatment.
	Concentrations	Dispersions prepared at nominal 0.013, 0.13, 1.3 and 13 g/L, untreated controls (note 1).
	Test conditions	72-h static test in algal medium; temperature: 22±1 °C; continuous illumination (9000-l 1000 lux); shaken at 100 rpm.
	Analysis	None.
	Phys. meas.	pH. Deviation ≤1.5 unit.
	Observations	Cell density at 72 h.

Results

Biological results

Parameter	Time [h]	Nominal concentration [g/L]				
		0	0.013	0.13	1.3	13
Mean cell density [10^4 cells/ml]	72	168	164	168	173	171
Inhibition [%]	*0-72*	*0*	*2*	*0*	*-3*	*-2*

Conclusions No conclusion about toxicity test substance (note 1).

Rev. note

1. A dispersion of the test substance was prepared with a homogeniser (10000 rpm, 2 minutes). The mixture was equilibrated for 24 hours and subsequently filtered. Further there was no information about the purity of the test substance. Since there were also no analytical measurements, the actual concentrations used in the test are not available. Probably the water system is not sensitive for the toxicity of the test substance due to its low solubility. No reliable LC50 value originates from this study.
2. The information in the report is limited to what is included in this summary. The pH-measurements, method of cell counting (only at 72 h) and growth inhibition were not further specified.

Klimisch criterium 3 No reliable LC50-value (note 1).

3.25

Title	Assessment of the algistatic effect of **CAS: 122-62-3.**
Date of report	April 15, 1994.
GLP	No.
Test substance	CAS: 122-62-3; purity not indicated.
Guideline	OECD 201.
Stat. method	Students t-Test
Test system	**Species** Green algae (*Scenedesmus subspicatus*).
	Initial cell conc. 1.9 x 10^4 cells/mL in controls.
	No. of replicates 6 per treatment, 3 for controls.
	Concentrations Water Accommodated Fractions (WAF) prepared at nominal 1000 mg/L (see note 1), untreated controls.
	Test conditions 72-h static test in 250 mL loosely stoppered flasks containing 100 mL of algal medium (pH 8.0); temperature: 24°C; continuous illumination (-7000 lux); continuously shaken at 100 rpm.
	Analysis At 0 and 72 h from control and 1000 mg/L by TOC-analysis.
	Phys. meas. pH. 8.0 at 0 h and 10.0-l 0.2 at 72 h.
	Observations Cell density at 0, 24, 48 and 72 h by spectrophotometry for treated flasks; control cultures at 0 and 72 h by counting with haemacytometer.
Results	For analytical results see 1st table below (note 4). Biological data are shown in the 2nd table (note 5).

Analytical results

	Concentration of TOC (mg C/L)	
Time (h)	**Control**	**Treatment**
0	1.74	2.07
72	4.62	4.34

Biological results

		Loading rate	WAF [mg/L]
Parameter	**Time [h]**	**0**	**1000**
Mean cell density [10^4 cells/ml]	0	1.9	1.9
	24	5.5	5.4
	48	14	13
	72	49	49
Inhibition [%] – AUC	0-72	0	1
Inhibition [%] -growth rate	0-72	0	0

Conclusions	Solubility of test substance is very low; no conclusion about toxicity test substance (note 4).
Rev. note	1. WAF is the maximum soluble concentration of the nominal test concentrations after 24 hours of stirring and 1 hour of equilibrating. Only the water phase was used in the definitive test solutions. In this test a WAF with a loading rate of 2000 mg/L was prepared, which was diluted with algal suspension to give a final WAF with a loading rate of 1000 mg/L.
	2. Strong rises in pH were recorded, probably associated with strong cell growth in the test (growth factor of 26 in 72 h).
	3. The amount of active ingredient (sebacic acid, bis(2-ethylhexyl)ester) in and the purity of CAS: 122-62-3 were not specified in the report.
	4. The analytical results show very low concentrations of the test substance in the test solutions at 0 h. At 72 h nothing is measured in the TOC analysis. This is probably due to the low solubility of the test substance in the water. Probably the water system is not sensitive for the toxicity of the test substance due to its low solubility. No reliable LC_{50} value originates from this study.
	5. The initial cell concentrations were only specified for the controls and were relatively high. For the treatment flasks only absorbance values were given to indicate cell growth during the test. In this summary cell densities are included, which are deduced from a calibration curve prepared by the reviewer using the measured cell densities for the control at 0 and 72 h. The growth inhibition was also recalculated by the reviewer using the method specified in OECD 201.
Klimisch criterium	3 No reliable LC50-value (note 4), test substance not specified (note 3).

GROUP C

3.26

Title	Five day algal assay	
Date of report	December 8, 1981.	
GLP	No.	
Test substance	CAS: 70729-68-9, purity: 88%, 6% triethylene glycol di-n-heptanoate, 4% mixed ester of tetraethylene glycol with n-heptanoic and 2 methylhexanoic acids, 2% other mixed esters.	
Guideline	Not indicated.	
Stat. method	Not indicated.	
Test system	**Species**	Green algae (*Selenastrum capricornutum*).
	Initial cell conc.	1 x 10^4 cells/mL.
	No. of replicates	4/treatment.
	Concentrations	Nominal: 25, 50, 100 mL/L (vehicle acetone), untreated and vehicle controls.
	Test conditions	120-h static test in 250 mL flasks containing 50 mL of algal medium (pH 7.1, hardness 18 mg $CaCO_3$/L); temperature: 24±2°C; continuous illumination (-4300 lux); continuously shaken at 100 rpm.
	Analysis	No analyses were performed.
	Phys. meas.	Not indicated.
	Observations	Cell density at least at 0 and 120 h by electronic particle counting, verified by spot haemacytometer counts (at 0 and 120 h).

Results

		Nominal concentration [mL/L]				
Parameter	**Time [h]**	**Control (untr)**	**Control (veh)**	**25**	*50*	**100**
Mean cell density [10^4 cells/ml]	120	21	*20*	*9.3*	*5.3*	*4.7*
Inhibition [%]	*0-120*	**0**	**2**	**55**	**74**	**77**

Conclusions 120 h-LC_{50} recalculated by the reviewer using regression analyses was 16 mL/L.

Rev. note

1. The concentrations were given in "mL/L". Since the density of the test substance is probably ~1 mg/mL, the LC_{50} was ~16 mg/L.
2. The test solutions were prepared from a 20% stock solution (1 mL test material and 4 mL of acetone). The concentrations of vehicle ranges from 10-40% (v/v). This is rather high (OECD 201, max. 100 mg/L = 13%). The amount of acetone in the control treatment was not reported, so it cannot be excluded that the test solutions contained more acetone than the vehicle control.
3. After 5 days the growth factor in the controls was only 20-21. OECD 201 stated that the growth factor in the control after 72 hours should be ≥16. Assuming exponential growth (characteristic of a healthy culture), a factor 20-21 is considered insufficient to meet this criterium. This invalidates the test.
4. The study report was essentially limited to what is included above. Individual replicate data and physical measurements were not reported.

Klimisch criterium 3 Insufficient growth in control (note 3), limited report (note 4).

GROUP D

No data available.

GROUP E

3.27

Title	Static 72-hour algae growth inhibition study of the WAF of **CAS: 11138-60-6** to *Raphidocelis subcapitata* (formerly, *Selenastrum capricomutum)*
Date of report	November 26, 1996.
GLP	Yes.
Test substance	CAS: 11138-60-6, purity 100%.
Guideline	OECD 201, EEC L383A/179-186 C 3 (1992).
Stat. method	Fischer's exact test and binomial probability analysis.
Test system	**Species** Green algae (*Raphidocelis subcapitata).* **Initial cell conc.** 1 x 10^4 cells/ml. **No. of replicates** 3 per treatment, 6 for controls. **Concentrations** Water Accommodated Fractions (WAF, see note 1) prepared at nominal 12, 24, 97, 242 and 1018 mg/L, untreated controls. **Test conditions** 72-h static test in 125 mL flasks containing 50 mL of algal medium (pH 7.5); temperature: 24±1 °C; continuous illumination (-5000 lux); continuously shaken at 100 rpm. **Analysis** At 0 and 72 h from control, 12, 97 and 1018 mg/L by extraction/GC-FID. **Phys. meas.** pH. At 72 h in all flasks 7.8-8.4. Temperature. Daily monitored, result not reported. **Observations** Cell density at 24, 48 and 72 h by counting with haemacytometer.
Results	For analytical results see 1 st table below (LOD 0.12 mg/L). Biological data are shown in the 2nd table.

Analytical results

	Measured concentration [mg/L]			
Time (h)	**0**	**12**	**97**	**1018**
0	nd	0.54	1.24	0.68
72	nd	nd	nd	nd

Biological results

		Nominal concentration [mg/L]					
Parameter	**Time [h]**	**0**	**12**	**24**	**97**	**242**	**1018**
Mean cell density [10^4 cells/ml]	24	8	8	7	7	7	4
	48	29	22	26	24	25	13
	72	129	106	106	114	122	82
Inhibition [%] – AUC	*0-72*	*0*	*18*	*15*	*13*	*8*	*44*
Inhibition [%] – growth rate	*0-72*	*0*	*4*	*4*	*3*	*1*	*9*

Conclusions	Solubility of test substance is very low; no conclusion about toxicity test substance (note 2).
Rev. note	1. WAF is the maximum soluble concentration of the nominal test concentrations after 20 hours of stirring and 4 hours of equilibrating. Only the water phase was used in the definitive test solutions. 2. The analytical results show very low concentrations of the test substance in the test solutions. This could partly be due to the inhomogeneity of the solution, but mostly to the very low solubility of the test substance in the water. Probably the water system is not sensitive for the toxicity of the test substance due to its low solubility. No reliable LC50 value originates from this study. 3. The growth inhibition was recalculated according to OECD 201 by the reviewer. 4. *Minor remarks* Light intensity and algae medium were not in accordance with OECD 201. The test is still acceptable, since no effects on the cell growth was seen in the controls.
Klimisch criterium	3 No reliable LC50-value (note 2).

3.28

Title The toxicity of **CAS: 68424-31-7 and 70983-72-l** to *Scenedesmus subspicatus*

Date of report March 27, 1996.

GLP Yes.

Test substance CAS: 68424-31-7 and 70983-72-l ; purity 100%.

Guideline OECD 201, 92/69/EEC L383A C3 (1992), ISO 8692:1989(E).

Stat. method Not specified.

Test system

Species Green algae *(Scenedesmus subspicatus).*

Initial cell conc. 8.2 x 1 0^3 cells/ml.

No. of replicates 3 per treatment, 6 for controls.

Concentrations Nominal 1, 1.8, 3.2, 5.6 and 10 mg/L (dispersions), untreated controls.

Test conditions 72-h static test in algal medium with illumination.

Analysis At 0 and 72 h from one replicate per treatment by extraction/GC-FID.

Phys. meas. pH. At 0 and 72 h in test solutions 6.8-7.9. Temoerature. 21-24°C.

Observations Cell density at 0, 24, 48 and 72 h by particle counting.

Results For analytical results see 1'" table below. Biological data are shown in the 2nd table.

Analytical results

	Measured concentration [% nominal]					
Time (h)	**0**	**1**	**1.8**	**3.2**	**5.6**	**10**
0	0.01 mg/L	70	61	66	59	61
72	0.05 mg/L	49	29	50	25	27
0-72	0.03 mg/L	60	45	58	42	44

Biological results

		Mean measured concentration [mg/L]					
Parameter	**Time [h]**	**0**	0.60	0.84	1.8	2.4	4.4
Mean cell density [10" cells/ml]	0	1	1	1	1	1	1
	24	4	3	3	4	4	3
	48	15	15	15	17	14	20
	72	68	67	70	88	70	101
Inhibition [%] – AUC	O-72	0	3	-2	-26	-1	-42
Inhibition [%] -growth rate	O-72	0	1	-5	-6	-3	-17

Conclusions 72 h-EC_{50} >4.4 mg/L.

Rev. note

1. In the report no information is available about the light regime and intensity. Neither is it clear whether aeration was performed. Since no effect on the control cell growth was seen, the circumstances during the study can be expected to be correct, or at least acceptable to create a valid test.
2. The growth inhibition was recalculated according to OECD 201 by the reviewer.

Klimisch criterium 1

3.29

Title The toxicity of **CAS: 126-57-6** *to Scenedesmus subspicatus*

Date of report July 30, 1996.

GLP Yes.

Test substance CAS: 126-57-8; purity 100%.

Guideline OECD 201, 92/69/EEC L383A C3 (1992), ISO 8692:1989(E).

Stat. method Not specified.

Test system

Species Green algae *(Scenedesmus subspicatus).*

Initial cell conc. 1 0^4 cells/ml.

No. of replicates 3 per treatment, 6 for controls.

Concentrations Nominal 0.1, 0.32, 1 .O, 3.2 and 10 mg/L (dispersions), untreated controls.

Test conditions 72-h static test in algal medium with illumination.

Analysis At 0, 24, 48 and 72 h from one replicate per treatment by extraction/GC-FID.

Phys. meas. pH. At 0 and 72 h in test solutions 7.2-9.5. Temperature. 21-23°C.

Observations Cell density at 0, 24, 48 and 72 h by particle counting and at 48 and 72 h by spectrophotometry.

Results For analytical results see 1st table below. Biological data are shown in the 2nd table.

Analytical results

	Measured concentration [% nominal]				
Time (h)	**0.1**	**0.32**	**1**	**3.2**	**10**
0	150	109	83	81	81
24	130	25	26	34	47
48	230	63	17	11	34
72	30	0	0	0	14
0-72	*135**	*49**	*32*	*32*	*44*

* Analytical results below 0.3 mg/L are not reliable (note 1)

Biological results

		Mean measured concentration [mg/L]					
Parameter	**Time [h]**	**0**	**0.14**	**0.16**	0.32	1.0	4.4
Mean cell density [10^4 cells/ml]	0	1	1	1	1	1	1
	48	11	8	8	8	6	2
	72	55	42	53	59	70	61
Inhibition [%] - AUC	O-72	0	26	10	5	-1	22
Inhibition [%] -growth rate	O-72	0	8	1	-1	-9	-2

Conclusions 72 h-EC_{50} >4.4 mg/L.

Rev. note

1. The method of analysis was not valid for concentrations below 0.3 mg/L, due to the LOD.
2. In the report no information is available about the light regime and intensity. Since no effect on the control cell growth was seen, the circumstances during the study can expected to be correct, or at least acceptable to create a valid test.
3. The result of the cell density at 24 hours was not reported. The growth inhibition was recalculated according to OECD 201 by the reviewer.
4. Strong rises in pH were recorded. Such rises are often associated with strong cell growth, probably due to CO:! depletion from test media. CO_2 exchange between the atmosphere and the test media is commonly facilitated by shaking the flasks. In the present test it is not clear whether the flasks were shaken. The control was not affected by lack of CO_2, since a very adequate growth factor of 55 in 72 hours was measured. So the study reliability is not lowered.

Klimisch criterium 1

Appendix 4 - Health Data for the Aliphatic Esters

Acute oral toxicity

GROUP A

4.03

Title Final report on the safety assessment of Octyl Palmitate, Cetyl Palmitate and Isopropyl Palmitate

Date of report 1982.

GLP No.

Test substance CAS: 29806-73-3, Octyl Palmitate, purity 98.6% (<1.4% palmitic acid).

Guideline Not indicated.

Stat. method Not applicable.

Test system

Species	rat	rat	rat
No. animals	**10**	5/dose group.	5/dose group
Dosage	Single oral administration of maximum 8 ml/kg (↔6900 mg/kg).	Single oral administration of 2.5, 5.0, 10.0, 20.0 or 40.0 ml/kg(↔2200, 4300, 8600, 17200 or 34400 mg/kg).	Single oral administration of 2.0, 4.0, 8.0, 16.0, 32.0 or 64.0 ml/kg(↔1700, 3400, 6900, 13800, 27500 or 55000 mg/kg).
Observations	Clinical signs and mortality.	Mortality.	Clinical signs and mortality.
Results	No clinical signs or mortality.	No mortality.	Clinical signs were seen in the 32.0 and 64.0 ml/kg dose group and consisted of wet rough fur, diarrhoea, ocular haemorrhage. No mortality.
LD50	> 6900 mg/kg.	> 34400 mg/kg.	> 55000 mg/kg

Conclusions Oral LD_{50} > 55000 mg/kg.

Rev. note
1. It is stated that both sexes were used.
2. Dose levels were re-calculated by the reviewer based on the density of the test substance (860 mg/ml).

Klimisch criterium 4 Limited report, secondary literature.

4.05

Title Toxicity studies for Union Camp Corporation.
Date of report October 6, 1972.
GLP No.
Test substance CAS: 68334-13-4, purity not indicated.
Guideline Not indicated.
Stat. method Not indicated.
Test system
Species Rat, weight 200-300 g.
No. of animals 5/treatment.
Dosage Single oral (gavage) administration of 2.0, 4.0, 8.0, 16.0, 32.0 or 64.0 g/kg; no controls; feeding *ad libitum* (food was withheld -24 h prior to dosing).
Observations Mortality/clinical signs daily for 14 days.

Results

Dose [g/kg bw] \ effect	Day	2.0	4.0	8.0	16.0	32.0	64.0	DR
Mortality	1-14	None						
Clinical signs(A)	1-14				+	+	+	X

(A) Sluggish and impaired locomotion, swelling around the ocular area, slight loss of hair and wet, messy, rough fur was noted.

Conclusions Oral LD_{50} > 64.0 g/kg body weight.
Rev. **note**
1. Each dose level consisted of 5 animals. Males and females were indicated to be distributed equally, but no further information on this subject was provided. It is not clear whether the animals were the animals were group-caged by sex.
2. The report was limited. No measurements of body weights or post-mortem investigation were performed.

Klimisch criterium 2 Limited report, non-GLP.

4.06

Title Toxicity studies for Union Camp Corporation.
Date of report July 13, 1972.
GLP No.
Test substance CAS: 29806-73-3, 2-Ethylhexyl palmitate, purity not indicated.
Guideline Not indicated.
Stat. method Not indicated.
Test system
Species Rat, weight 200-300 g.
No. of animals S/treatment.
Dosage Single oral (gavage) administration of 2.0, 4.0, 8.0, 16.0, 32.0 or 64.0 g/kg; no controls; feeding *ad libitum* (food was withheld -24 h prior to dosing).
Observations Mortality/clinical signs daily for 14 days.

Results

Dose [g/kg bw] \ effect	Day	2.0	4.0	6.0	16.0	32.0	64.0	DR
Mortality	1-14	None						
Clinical signs(A)	1-14					+	+	x

(A) Diarrhoea, ocular haemorrhage and wet, rough fur was noted. Animals returned to normalcy within five days.

Conclusions Oral LD_{50} > 64.0 g/kg body weight.
Rev. note
1. Each dose level consisted of 5 animals. Males and females were indicated to be distributed equally, but no further information on this subject was provided. It is not clear whether the animals were group-caged by sex.
2. The report was limited. No measurements of body weights or post-mortem investigation were performed.

Klimisch criterium 2 Limited report, non-GLP.

4.07

Title Single dose oral toxicity in rats

Date of report August 19, 1982.

GLP NO.

Test substance CAS: 29806-73-3, Octyl palmitate, purity not indicated.

Guideline Not indicated.

Stat. method Not indicated.

Test system

Species Rat (Wistar), weight 213 - 230 g.

No. of animals 10 males/treatment.

Dosage Single oral administration of 5000 mg/kg bw (dosing volume not indicated): no controls; feeding ad *libitum* (food was withheld -16 20 h prior to dosing).

Observations Mortality and clinical signs several times on day 0 (day of dosing) and daily until day 14.

Results

Dose [mg/kg bw]\effect		5000
Sex	Day	M
Mortality	o-14	1/10
Clinical signs(A)	o-14	+

(A) Clinical signs included chromodacryorrhea, lethargy, piloerection, diarrhoea, ptosis and wet anogenital area.

Conclusions Oral LD_{50} > 5000 mg/kg bw.

Rev. note

1. No body weight measurements were performed during the study.
2. No necropsy was performed at termination.

Klimisch criterium 2 Limited report. Non-GLP study.

GROUP B

4.08

Title Range-Finding Toxicity Data: List VI

Date of report March-April, 1962.

GLP No.

Test substance CAS: 103-24-2, purity not indicated .

Guideline Not indicated.

Stat. method Thompson, Weil.

Test system

Species Rat (Carworth-Wistar), males, weight 90- 120 g, 4 - 5 weeks of age.

No. of animals 5/treatment.

Dosage Single oral administration (gavage), dose levels not given (vehicle not indicated: water, corn oil of Tergitol, dose volume not given); use of control group not given, animals were non-fasted.

Observations Mortality during 14 days.

Conclusions Oral LD_{50} : 8.72 ml/kg

Rev. note

1. No measurements for clinical signs, body weights, food consumption and necropsy were performed during the study. No results of the mortalities were given.
2. The report was limited to the above mentioned. Density is not given, therefore the dose in mg/kg could not be calculated by the reviewer.

Klimisch criterium 4 Very limited report. Non-GLP study.

4.09

Title Range-Finding Toxicity Data: List V
Date of report 1954.
GLP No.
Test substance CAS: 105-52-2, purity not indicated .
Guideline Not indicated.
Stat. method Thompson, Weil.
Test system
Species Rat (Carworth-Wistar), males, weight 90-120 g, age not given.
No. of animals 5/treatment.
Dosage Single oral administration (gavage), dose levels not given (vehicle not indicated: water, corn oil of Tergitol), dose volume between 1 and 10 mL); use of control group not given, animals were non-fasted.
Observations Mortality during 14 days.
Conclusions Oral LD_{50} : 7.46 g/kg.
Rev. note
1. No measurements for clinical signs, body weights, food consumption and necropsy were performed during the study. No results of the mortalities were given.
2. Information about several aspects was incomplete or absent.

Klimisch criterium 4 Very limited report. Non-GLP study.

4.10

Title Problems of hygiene maintenance for food coming into contact with rubber and plastics products
Date of report 1975.
GLP No.
Test substance CAS: 27178-l 6-1, Di-isodecyl adipate, purity not indicated.
Guideline Not indicated.
Stat. method Not applicable.
Test system
Species Rat.
Dosage Oral.
Conclusions Oral LD_{50} 20.5 g/kg.
Klimisch criterium 4 Limited report, secondary literature.

4.11

Title Acute oral toxicity study
Date of report December 11, 1973.
GLP No.
Test substance CAS: 16958-92-2, purity not indicated.
Guideline Not indicated.
Stat. method Not applicable.
Test system
Species Rat (Sherman-Wistar).
No. of animals 5/sex/treatment.
Dosage Single oral administration of 16.0 g/kg; no controls; feeding *ad libitum* (food was withheld -24 h prior to dosing).
Observations Mortality/clinical signs daily for 14 days.

Results

Dose [g/kg bw] \ effect	**Day**	*16.0*	
Sex		**M**	**F**
Mortality	1-14	None	

Conclusions Oral LD_{50} > 16.0 g/kg.
Rev. **note** Report was limited. No measurements for body weight or clinical signs were reported. No necropsy was performed.
Klimisch criterium 2 Limited report, non-GLP.

4.12

Title	Report on single dose oral toxicity in rats.	
Date of report	March 27, 1978.	
GLP	No.	
Test substance	CAS: 16958-92-2, name and purity not indicated.	
Guideline	Not indicated.	
Stat. method	Not indicated.	
Test system	**Species**	Rat (Wistar), weight 200-300 g.
	No. of animals	5/sex/treatment.
	Dosage	Single oral administration of 15.0 g/kg; no controls; feeding ad *libitum* (food was withheld -18 h prior to dosing).
	Observations	Clinical signs for 14 days.

Results

Dose [g/kg bw] \ effect	**15.0**	
Sex	**M**	**F**
Mortality	None	
Clinical Signs(A)	++	+

(A) Clinical sians consisted of diarrhoea, lethargy, flaccid, body oily, ptosis and chromorhinnorrhea.

Conclusions	Oral LD_{50} > 15.0 g/kg.
Rev. note	The report was limited. No measurements of body weights or necropsy were performed.
Kiimisch criterium	2 Limited report, non-GLP.

4.13

Title	Toxicity studies for XXXX	
Date of report	October 6, 1972.	
GLP	No.	
Test substance	CAS: 108-63-4, purity not indicated.	
Guideline	Not indicated.	
Stat. method	Not indicated.	
Test system	**Species**	Rat, weight 200-300 g.
	No. of animals	5/treatment.
	Dosage	Single oral (gavage) administration of 2.0, 4.0, 8.0, 16.0, 32.0 or 64.0 g/kg; no controls; feeding ad *libitum* (food was withheld -24 h prior to dosing).
	Observations	Mortality/clinical signs daily for 14 days.

Results

Dose [g/kg bw] \ effect	**Day**	**2.0**	**4.0**	**8.0**	**16.0**	**32.0**	**64.0**	**DR**
Mortality	1-14	0/5	0/5	0/5	0/5	0/5	2/5	x
Clinical signs(A)	1-14			+	+	+	+	x

(A) Sluggish locomotion, lethargy, ocular swelling and wet, scrufty, rough fur was noted. Survivors returned to normalcy within seven days.

Conclusions	Oral LD_{50} > 64.0 g/kg body weight.
Rev. note	1. Each dose level consisted of 5 animals. Males and females were indicated to be distributed equally, but no further information on this subject was provided. It is not clear whether the animals were group-caged by sex. 2. The report was limited. No measurements of body weights or post-mortem investigation were performed.
Klimisch criterium	2 Limited report, non-GLP.

4.14

Title Range finding toxicity tests.
Date of report January 12, 1977.
GLP No.
Test substance CAS: 142-16-5 (di-2-ethylhexyl maleate), purity 100%.
Guideline Not indicated.
Stat. method Not applicable.
Test system
Species Rat (Hilltop-Wistar), mean weight 98-l 07 g.
No. of animals 13 males.
Dosage Single oral administration of 10.0 ml/kg to 10 males and of 5.0 ml/kg to 3 males; no controls; feeding *ad libitum.*
Observations Mortality/clinical signs twice on day 1, daily from day 2 to 8, and on day 14.
Body weights on day 1 and 14.
Necropsy on day 14.

Results

Dose [ml/kg bw] \ effect	Day	5.0	10.0
Mortality	1-14	None	
Clinical signs[(A)]	l-14		+
Body weight gain	1-14	No treatment related effects	
Necropsy	14	No treatment related effects	

[(A)] Findings consisted of wet fur.

Conclusions Oral LD_{50} > 10.0 ml/kg.
Rev. note
1. No measurements for body weight on day 7 were performed.
2. The animals were not fasted before treatment.
3. Dose level (g/kg) could not be calculated, since density was not indicated.
4. 13 males were used instead of 5/sex/dose group.

Klimisch criterium 2 Report was limited to the above mentioned, non-GLP.

4.15

Title Acute Oral Toxicity Test of **"CAS: 28472-97-l"** in Rats
Date of report December 22, 1993.
GLP **Yes.**
Test substance CAS: 28472-97-1, purity: not indicated.
Guideline OECD 401, 92/69/EEC.
Stat. method Not applicable.
Test system
Species Rat (Wistar), weight males 209-221 g, females 153-l 89 g.
No. of animals 5/sex/treatment.
Dosage Single oral administration (gavage) of 2000 mg/kg bw (dosing volume 2.20 ml/kg); no controls; feeding *ad libitum* (food was withheld -16 h prior to dosing and -3 - 4 h after dosing).
Observations Mortality and clinical signs several times on day 0 (day of dosing) and daily until day 14.
Body weights on day 0, 7 and 14.
Necropsy on day 14.

Results

Dose [mg/kg bw]\effect		2000	
Sex	Day	M	F
Mortality	o-14	None	
Clinical signs	o-14	No treatment related effects	
Body weight gain	o-14	No treatment related effects	
Necropsy[(A)]	14	No treatment related effects	

(A) Incidental findings included urinary retention in the bladder, hyperaemia in the lung and hyrometra of the uterus.

Conclusions Oral LD_{50} > 2000 mg/kg bw.
Klimisch criterium 1

GROUP C

4.16

Title Final report on the safety assessment of Glycol Stearate, Glycol Stearate SE, and Glycol Distearate

Date of report 1982.

GLP No.

Test substance CAS: 627-83-8, Glycol Distearate, purity not indicated.

Guideline Not indicated.

Stat. method Not applicable.

Test system

Species	rat	rat	rat	rat
No. animals	5/dose	5/dose	1 O/dose	1 O/dose
Dosage	Single oral administration of 0.464-l 0 g/kg (50% in corn oil)	Single oral administration of 0.5-l 6 g/kg (25% in corn oil)	Single oral administration of 10 g/kg	Single oral administration of 5000 mg/kg (undiluted)
Observations	Not indicated			
Results	Doses of 13 or more g/kg bw in corn oil produced diarrhoea, wet oily coats, and nasal haemorrhage.			
LD50	> 10 g/kg	> 16 g/kg	> 10 g/kg	> 5000 mg/kg

Conclusions Oral LD_{50} > 16 g/kg.

Klimisch criterium 4 Limited report, secondary literature.

4.17

Title Acute oral toxicity and primary skin and eye irritation studies of **CAS: mix of 67989-24-6 and 70024-57-6** and industrial phosphate ester

Date of report December 30, 1976.

GLP No.

Test substance CAS: 67989-24-6 and 70024-57-6 (both 40-45%), **CAS: mix of 67969-24-6 and 70024-57-6**, impurities polymerised quinoline and styrene co-polymer (both 1-5%).

Guideline Not indicated.

Stat. method Not applicable.

Test system

Species Rat, weight 215-229 g.

No. of animals 5 males/dose group.

Dosage Single oral administration (gavage) of 0.464, 1 .00, 2.15, 4.64 and 10.0 ml/kg bw; no controls; feeding ad *libitum* (food was withheld -18 h prior to dosing).

Observations Mortality/clinical signs several times on day 1 and at least once daily for 14 days.
Body weights on day 1 and 14.
Necropsy on day 14.

Results

Dose [ml/kg bw] \ effect	**Day**	**0.464**	**1 .OO**	**2.15**	**4.64**	**10.0**	**DR**
Mortality	1-14	None					
Clinical signs[(A)]	1-14			+	+	+	x
Body weight gain	1-14	No treatment related effects					
Necropsy	14	No treatment related effects					

[(A)] Clinical observations included diarrhoea, staining of urine or diarrhoea, oily rough, unkempt fur, depression, depressed righting and placement reflexes.

Conclusions Oral LD_{50} > 10.0 ml/kg bw.

Rev. note
1. 5 males/dose group were used instead of 5/sex/dose group.
2. Density was not indicated, so doses in mg/kg could not be calculated.
3. *Minor remarks.* No measurements of body weight were performed on day 7.

Klimisch criterium 2 Report was limited to the above mentioned, non-GLP.

4.18

Title Acute oral toxicity and primary skin and eye irritation studies of **CAS: mix of 67989-24-6 and 70024-57-6**

Date of report December 30, 1976.

GLP No.

Test substance CAS: 67989-24-6 and 70024-57-6 (mix tested), purity not indicated.

Guideline Not indicated.

Stat. method Not applicable.

Test system

Species Rat, weight 205-237 g.

No. of animals 5 males/dose group.

Dosage Single oral administration (gavage) of 0.464, 1 .00, 2.15, 4.64 and 10.0 ml/kg bw; no controls; feeding *ad libitum* (food was withheld -18 h prior to dosing).

Observations Mortality/clinical signs several times on day 1 and at least once daily for 14 days.
Body weights on day 1 and 14.
Necropsy on day 14.

Results

Dose [ml/kg bw] \ effect	Day	0.464	1 .OO	2.15	4.64	10.0	DR
Mortality	1-14	None					
Clinical signs[A]	1-14			+	+	+	x
Body weight gain	1-14	No treatment related effects					
Necropsy	14	No treatment related effects					

[A] Clinical observations included diarrhoea, oily rough fur, depression, depressed righting and placement reflexes.

Conclusions Oral LD_{50} > 10.0 ml/kg bw.

Rev. note
1. 5 males/dose group were used instead of 5/sex/dose group.
2. Density was not indicated, so doses in mg/kg could not be calculated.
3. *Minor remarks. No* measurements of body weight were performed on day 7.

Klimisch criterium 2 Report was limited to the above mentioned, non-GLP.

4.19

Title Oral LD50 test in rats

Date of report April 7, 1981.

GLP No.

Test substance CAS: 70729-68-9, purity: 88%, 6% triethylene glycol di-n-heptanoate, 4% mixed ester of tetraethylene glycol with n-heptanoic and 2 methylhexanoic acids, 2% other mixed esters; used undiluted or 55-90% formulation in corn oil.

Guideline Not indicated.

Stat. method Probit analysis (Finney, 1971).

Test system

Species Rat (Crl:CD), weight 187-203 g.

No. of animals 10 females/treatment.

Dosage Single oral administration (gavage) of 14, 19, 22, 23, 24, 24.5, 24.75, 24.9 and 25 g/kg bw (vehicle corn oil); dosing volume 4.3-5.0 mL (at 25 g/kg bw; 8.9 mL in two times); no controls.

Observations Mortality/clinical signs/body weight until day 14.

Results

Dose [g/kg bw] \ effect	Day	14	19	22	23	24	24.5	24.75	24.9	25	DR
Mortality[A]	o-14	0/10	0/10	0/10	0/10	4/10	1/10	1/10	2/10	10/10	x
Clinical signs[B]	o-14	+	+	+	+	+	+	+	+	+	
Body weight	14	d	d	d	d	d	d	d	d	d	

(A) All deaths occurred within 2 days
(B) Clinical observations included flat body posture, moribundness, labored breathing, stained/wet perineal area, lacrimation, stained face, weakness, ataxia, lethargy, prostration, salivation and chromodacryorrhea.

Conclusions Oral LD_{50} 25 g/kg bw.

Rev. note
1. Only females are used in this test.
2. The frequency of the observations was not indicated. No individual values were presented. It is not clear whether or not fed was witheld before dosing. No necropsy was performed.
3. The report is limited to the above mentioned.

Klimisch criterium 2 Limited report, only females tested.

4.20

Title Acute oral toxicity test of CAS: 70729-68-g in rats

Date of report July 5, 1991.

GLP Yes.

Test substance CAS: 70729-68-9, purity 94.5%, 2% monoesters.

Guideline OECD 401, 84/449/EEC.

Stat. method Not applicable.

Test system

Species Rat (Wistar), weight males 281-l 95 g, females 165-181 g.

No. of animals 5/sex/treatment.

Dosage Single oral administration (gavage) of 2000 mg/kg bw (dosing volume 2 mL/kg); no controls; fed was withheld 16 h prior to dosing and 3-4 h thereafter.

Observations Mortality/clinical signs 10 min, 1, 2, 6 and 24 h post-dosing and daily thereafter for 14 days.
Body weight on day 0, 7 and 14.
Necropsy on day 14.

Results

Dose [mg/kg bw]\effect	Day	2000
Mortality	o-14	None
Clinical signs(A)	o-14	+
Body weight	o-14	No treatment related effects
Necropsy	14	No treatment related effects

(A) Clinical signs observed on day 1 only included ventral or limb position, reduced activity, reduced skin tugor and &erection.

Conclusions Oral LD_{50} >2000 mg/kg bw.

Klimisch criterium 1

4.21

Title Oral LD50 test in rats

Date of report July 23, 1980.

GLP No.

Test substance CAS: 70729-68-9, purity: 88%, 6% triethylene glycol di-n-heptanoate, 4% mixed ester of tetraethylene glycol with n-heptanoic and 2 methylhexanoic acids, 2% other mixed esters.

Guideline Not indicated.

Stat. method Not applicable.

Test system

Species Rat (ChR:CD), weight 261 g.

No. of animals 10 males/treatment.

Dosage Single oral administration (gavage) of 25 g/kg; dosing volume 6.5 mL in two times; no controls.

Observations Mortality/clinical signs/body weight until day 14.

Results

Dose [g/kg bw]\effect	Day	25
Mortality(A)	O-14	1/10
Clinical signs(B)	O-14	+
Body weight	1 4	Not reported

(A) Death occurred on the day after dosing.
(B) Clinical observations included hyperaemia, lethargy and prostration.

Conclusions Oral LD_{50} >25 g/kg bw.

Rev. note
1. Only males are used in this test.
2. The frequency of the observations was not indicated. No individual values were presented. It is not clear whether or not feed was witheld before dosing. No necropsy was performed.
3. Slight initial weight loss was observed.
4. The report is limited to the above mentioned.

Klimisch criterium 2 Limited report, only males tested.

GROUP D

4.22

Title Final report on the safety assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate

Date of report 1985.

GLP No.

Test substance CAS: 1338-41-6, Sorbitan stearate, purity not indicated.

Guideline Not indicated.

Stat. method Not applicable.

Test system

Species	rat	rat	Rat (Harlan Wistar)
No. animals	10/sex	5 females	5/sex
Dosage	Single oral dose (gavage) of 15.9 g/kg (30%)	Single oral dose (gavage) of 15 g/kg (100%)	Single oral dose (gavage) of 0.28 g/kg (4%) (7 ml/kg) to fasted rats
Observations	Mortality for 14 days	Mortality, abnormalities for 7 days. Necropsy	Mortality, clinical signs for 14 days
Results	No mortality	No mortality or abnormalities	No mortality or clinical signs
LD50	> 15.9 g/kg	> 15 g/kg	> 0.28 g/kg

Conclusions Oral LD_{50} > 15.9 g/kg.

Klimisch criterium 4 Limited report, secondary literature.

4.23

Title Final report on the safety assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate

Date of report 1985.

GLP No.

Test substance CAS: 1338-39-2, Sorbitan laurate, purity not indicated.

Guideline Not indicated.

Stat. method Not applicable.

Test system

Species	rat	rat	rat	rat
No. animals	10 males	30 males	30 females	60/sex
Dosage	Single oral dose of 20 g/kg (100%)	Single oral dose of 25.1-39.8 g/kg (100%) to fasted rats	Single oral dose of 25.1-39.8 g/kg (100%) to fasted rats	Single oral dose of 25.1-39.8 g/kg (100%) to fasted rats
Observations	mortality for 2 days	mortality for 14 days	mortality for 14 days	mortality for 14 days
Results	no effects	2 of 10 rats died from highest dose		
LD50	> 20 g/kg	> 39.8 g/kg	33.6 g/kg	41.25 g/kg

Conclusions Oral LD_{50} > 41.25 g/kg.
Klimisch criterium 4 Limited report, secondary literature.

4.24
Title Final report on the safety assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate
Date of report 1985.
GLP No.
Test substance CAS: 8007-43-0, Sorbitan sesquioleate, purity not indicated.
Guideline Not indicated.
Stat. method Not applicable.
Test system

Species	rat	rat
No. animals	10/sex	2/sex
Dosage	Single oral dose of 39.8 g/kg (90%)	Single oral dose of 23.1 and 34.6 g/kg (3%)
Observations	Mortality for 14 days	Mortality, clinical signs for > 3 days
Results	No mortality	No mortality. Clinical signs consisted of hypoactivity and ruffled fur.
LD50	> 39.8 g/kg	> 34.6 g/kg

Conclusions Oral LD_{50} > 39.8 g/kg.
Klimisch criterium 4 Limited report, secondary literature.

4.25
Title Final report on the safety assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate
Date of report 1985.
GLP No.
Test substance CAS: 1338-43-8, Sorbitan oleate, purity not indicated.
Guideline Not indicated.
Stat. method Not applicable.
Test system

Species	rat	rat
No. animals	10/sex	males
Dosage	Single oral dose (gavage) of 39.8 g/kg (90%) to fasted rats	Single oral dose of 10 ml/kg (100%) ↔ 10 g/kg
Observations	Mortality for 14 days	Mortality for 6 days, histological examination
Results	No mortality	No mortality or abnormalities
LD50	> 39.8 g/kg	> 10 g/kg

Conclusions Oral LD_{50} > 39.8 g/kg.
Klimisch criterium 4 Limited report, secondary literature.

4.26

Title	Final report on the safety assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate
Date of report	**1985.**
GLP	**No.**
Test substance	CAS: 26266-58-0, Sorbitan trioleate, purity not indicated.
Guideline	Not indicated.
Stat. method	Not applicable.

Test system

Species	rat	Harlan Wistar rat
No. animals	**1 O/sex**	**5/sex**
Dosage	Single oral dose (gavage) of 39.8 g/kg (90%) to fasted rats	Single oral dose of 5.0 ml/kg (5%) ↔ 0.25 ml/kg (density not indicated)
Observations	Mortality for 14 days	Mortality, clinical signs for 7 days
Results	No mortality	No mortality or clinical signs
LD50	> 39.8 g/kg	> 0.25 ml/kg

Conclusions	Oral LD_{50} > 39.8 g/kg.
Klimisch criterium	4 Limited report, secondary literature.

4.27

Title	Oral toxicities of lauric acid and certain lauric acid derivatives
Date of report	1960.
GLP	**No.**
Test substance	CAS: 1338-39-2, CAS: 1338-39-2, purity not indicated.
Guideline	Not indicated.
Stat. method	Not indicated.
Test system	**Species** Rat (Osborne-Mendel), weight 40-50 g.
	No. of animals **1** O/sex/dose level.
	Dosage Dietary administration for 23 weeks at 0, 15, 20 and 25%; diets were prepared every two weeks.
	Observations Mortality/clinical signs (frequency not indicated). Body weights weekly. Blood parameters from at least 5 animals/dose level. Macroscopy and organ weights in survivors. Histopathology of all animals.

Results

Dose (% in diet)	**0**		**15**		**20**		**25**		**DR**	
Dose (g/kg bw)	**0**	**0**	**9**	**18**	**22**	**23**	**N/A**	**N/A**		
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Mortality			None				9/10	9/10		
Clinical signs(A)			+	+	+	+	+	+		
Body weight gain			dc	dc	dc	dc	N/A	N/A	x	
Haematology			Not reported							
Organ weight			Not reported							
Necropsy(B)			+	+	+	+	+	+	x	x
Histopathology(C)			+	+	+	+	+	+		

(A) Among treated animals diarrhoea and unkempt appearance was noted.
(B) Observations included gangrene of the tail, paleness and enlargement of the liver and bile duct enlargement.
(C) Among 31 animals investigated the main findings included fatty changes or fibrosis of the liver, chronic hepatitis, focal necrosis and/or slight or moderate enlargement of hepatocytes, thickening of the bile duct wall with enlargement, slight to moderate epithelial proliferation (minimal inflammation), focal nephritis (mainly in conical tubulus), proteinuria, foamy macrophages in the lungs and hyperplasia of bone-marrow and spleen.

Conclusion NOAEL < 23 g/kg bw.

Rev. note
1. The test substance is not sufficiently identified.
2. The high dose levels tested may interfere with nutritional balance of the diet. Therefore it can not be excluded that part of the observations may have been caused by this nutritional imbalance.
3. The diet was not analysed for adequacy and homogeneity of preparation and no information on stability of the test substance (in the matrix) was provided.
4. The report is limited to the above mentioned.

Klimisch criterium 3 Nutritional imbalance not excluded (note 2), limited report and no identity of the test substance.

4.2%

Title CAS: 1338-39-2 products — Acute oral toxicity in rats.

Date of report January 26, 1967.

GLP No.

Test substance CAS: 1338-39-2, purity not indicated.

Guideline Not indicated.

Stat. method Litchfield and Wilcoxon.

Test system

Species Rat (Wistar), weight males 134-l 67 g, females 140-l 57 g.

No. of animals 11 females and 10 males for the highest dose group and 5/sex for the other dose groups.

Dosage Single oral (gavage) administration (in two equal portions) of 28.2, 31.6, 35.5 and 39.8 g/kg (dosing volume 50 ml/kg); no controls; feeding ad *libitum* (food was withheld -16 h prior to dosing).

Observations Mortality on day 1, 2 and 14.
Clinical signs several times on day 1 and daily until day 14.
Body weights on day 1.
Necropsy on day 14.

Results

Dose [g/kg bw] \ effect		28.2		31.6		35.5		39.8		DR
Sex	Day	M	F	M	F	M	F	M	F	MF
Mortality	1-14	0/5	1/5	1/5	1/5	3/5	4/5	0/10	10/1 1	x
Clinical signs[A]	1-14	+	+	+	+	+	+	+	+	x x
Necropsy[B]	14	+	+	+	+	+	+	+	+	x x

(A) Clinical observations included depression, pallor, (mucoid) diarrhoea, ruffed fur, slight gasping, red discharge around eyes, in nose and mouth and wet, stained perineal area.

(B) Main findings in animals that died included autolysis, red, congested lungs with focal haemorrhages, hydronephrosis, pale, congested (medulla) kidneys, kidney necrosis, congestion of thymus, gas distended gastrointestinal tract, stomach erosion and congestion, congestion of intestines (fluid filled), pale, mottled liver, soft heart, engorged auricles of the heart. In 14-day survivors effects were limited to congestion of the lungs, soft and/or enlarged heart, hydronephrosis and congestion of the medulla.

Conclusions Oral LD_{50} 36.0 g/kg.

Rev. note The report was limited. No measurements for body weights were performed on days 7 and 14.

Klimisch criterium 2 Limited report, non-GLP.

4.29

Title CAS: 26266-58-O products-Acute oral toxicity in rats.
Date of report January 26, 1967.
GLP No.
Test substance CAS: 26266-58-0, purity not indicated.
Guideline Not indicated.
Stat. method Not applicable.
Test system
Species Rat (Wistar), weight 134-I 64 g.
No. of animals 1 O/sex/dose group.
Dosage Single oral (gavage) administration (in two equal portions) of 39.8 g/kg (dosing volume 50 ml/kg); no controls; feeding *ad libitum* (food was withheld -16 h prior to dosing).
Observations Mortality on day 1, 2 and 14.
Clinical signs several times on day 1 and daily until day 14.
Body weights on day 1.
Necropsy on day 14.

Results

Dose [g/kg bw] \ effect	39.8	
Sex	M	F
Mortality/Clinical signs	None	
Necropsy[A]	+	+

(A) Findings consisted of soft heart, hydronephrosis, focal haemorrhage in the lungs and congested lungs.

Conclusions Oral LD_{50} > 39.8 g/kg.
Rev. note The report was limited. No measurements for body weights were performed on days 7 and 14.
Klimisch criterium 2 Limited report, non-GLP.

4.30

Title Acute oral toxicity of CAS: 1338-39-2 products in rats.
Date of report November 23, 1966.
GLP No.
Test substance CAS: 1338-39-2, purity not indicated.
Guideline Not indicated.
Stat. method Litchfield and Wilcoxon.
Test system
Species Rat (Wistar), weight males 143-I 59 g, females 144-I 66 g.
No. of animals 5/sex treatment and 10/sex at the highest dose.
Dosage Single oral (gavage) administration (in two equal portions) of 25.1, 28.2, 31.6, 35.5 and 39.8 g/kg (dosing volume 50 ml/kg); no controls; feeding *ad libitum* (food was withheld -16 h prior to dosing).
Observations Mortality on day 1, 2 and 14.
Clinical signs several times on day 1 and daily until day 14.
Body weights on day 1.
Necropsy on day 14.

Results

Dose [g/kg bw] \ effect		25.1		28.2		31.6		35.5		39.8		DR	
Sex	Day	M	F	M	F	M	F	M	F	M	F	M	F
Mortality	I-14	0/5	0/5	0/5	2/5	0/5	3/5	0/5	1/5	2/10	9/10	x	x
Clinical signs[A]	1-14	+	+	+	+	+	+	+	+	+	+	x	x
Necropsy[B]	14	+	+	+	+	+	+	+	+	+	•t	x	x

(A) Clinical observations included depression, pallor, (mucoid) diarrhoea, hypersensitivity, ruffed fur, and wet perineal area.
(B) Main findings in animals that died included autolysis, pale, mottled liver, distended stomach and gastrointestinal tract, pale kidneys, congested medulla kidneys, hydronephrosis, cherry red, congested lungs with haemorrhage and congested thymus, stomach, heart or adrenals. Effects in 14-day survivors were soft heart, hydronephrosis, pale cortex kidneys, urine distended bladder, granular spleen, congested lungs with haemorrhages, diaphragmatic hernia and congested medulla kidneys.

Conclusions Oral LD_{50} 41.3 g/kg.
Rev. note The report was limited. No measurements for body weights were performed on days 7 and 14.
Klimisch criterium 2 Limited report, non-GLP.

4.31

Title	Acute oral toxicity of CAS: 1338-41-6 products in rats.	
Date of report	November 23, 1966.	
GLP	**No.**	
Test substance	CAS: 1338-41-6, purity not indicated.	
Guideline	Not indicated.	
Stat. method	Not applicable.	
Test system	**Species**	Rat (Wistar), weight 140-l 64 g.
	No. of animals	10 males/dose group, 11 females/dose group.
	Dosage	Single oral (gavage) administration(in two equal portions) of 15.9 g/kg (dosing volume 50 ml/kg); no controls; feeding ad *libitum* (food was withheld -16 h prior to dosing).
	Observations	Mortality on day 1, 2 and 14. Clinical signs several times on day 1 and daily until day 14. Body weights on day 1. Necropsy on day 14.

Results

Dose [g/kg bw] \ effect	**15.9**	
Sex	**M**	**F**
Mortalitv/Clinical signs	None	
Necropsy(A)	+	+

(A) Findings consisted of soft heart, bladder distended with urine, hydronephrosis, irregularly shaped kidneys, pale medulla of the kidneys, areas of pale discoloration in the kidneys, slight focal haemorrhage in the lungs and slight congested lungs.

Conclusions	Oral LD_{50} > 15.9 g/kg.
Rev. note	The report was limited. No measurements for body weights were pet-formed on days 7 and 14.
Klimisch criterium	2 Limited report, non-GLP.

4.32

Title	Acute oral toxicity of **Code 13** products in rats.	
Date of report	November 23, 1966.	
GLP	No.	
Test substance	CAS: 1338-43-8, purity not indicated.	
Guideline	Not indicated.	
Stat. method	Not applicable.	
Test system	**Species**	Rat (Wistar), weight 140-l 64 g.
	No. of animals	1 O/sex/dose group.
	Dosage	Single oral (gavage) administration (in two equal portions) of 39.8 g/kg (dosing volume 50 ml/kg); no controls; feeding ad *libitum* (food was withheld -16 h prior to dosing).
	Observations	Mortality on day 1, 2 and 14. Clinical signs several times on day 1 and daily until day 14. Body weights on day I. Necropsy on day 14.

Results

Dose [g/kg bw] \ effect	**39.8**	
Sex	**M**	**F**
Mortality	None	
Clinical signs(A)	+	+
Necropsy(B)	+	+

(A) Clinical observations included diarrhoea and wet perineal area.
(B) Findings consisted of soft heart, hydronephrosis, slight congestion of medulla of the kidneys, mucosa of the stomach reddened, (focal) congestion of the lungs, bladder distended with urine, mottled liver, mesenteric lymph nodes congested or hard, and (congenital) diaphragmatic hernia.

Conclusions	Oral LD_{50} > 39.8 g/kg.
Rev. note	The report was limited. No measurements for body weights were performed on days 7 and 14.
Klimisch criterium	2 Limited report, non-GLP.

4.33

Title	Acute oral toxicity of CAS: 26266-58-O products in rats.	
Date of report	November 23, 1966.	
GLP	No.	
Test substance	CAS: 26266-58-O, purity not indicated.	
Guideline	Not indicated.	
Stat. method	Not applicable.	
Test system	**Species**	Rat (Wistar), weight 140-l 64 g.
	No. of animals	1 O/sex/dose group.
	Dosage	Single oral (gavage) administration (in two equal portions) of 39.8 g/kg (dosing volume 50 ml/kg); no controls; feeding *ad libitum* (food was withheld -16 h prior to dosing).
	Observations	Mortality on day 1, 2 and 14. Clinical signs several times on day 1 and daily until day 14. Body weights on day 1. Necropsy on day 14.

Results

Dose [g/kg bw] \ effect	39.8	
Sex	M	F
Mortality	None	
Clinical signs[A]	+	+
Necropsy[B]	+	+

(A) Clinical observations included (mucoid) diarrhoea and wet perineal area.
(B) Findings consisted of soft heart, hydronephrosis, congested medulla of the kidneys, mucosa of the stomach reddened, slight congested lungs, bladder distended with urine, slightly granular spleen, and areas of dark discoloration in the pancreas.

Conclusions	Oral LD_{50} > 39.8 g/kg.
Rev. note	The report was limited. No measurements for body weights were performed on days 7 and 14.
Klimisch criterium	2 Limited report, non-GLP.

4.34

Title	*CAS:* **1338-43-8**: acute oral toxicity study in male and female rats	
Date of report	November 23, 1966.	
GLP	No.	
Test substance	CAS: 1338-43-8, purity: not indicated.	
Guideline	Not indicated.	
Stat. method	Not indicated.	
Test system	**Species**	Rat (Wistar), weight males 144 - 154 g, females 135 - 154g.
	No. of animals	1 O/sex/treatment.
	Dosage	Single oral administration (gavage) of 39800 mg/kg bw (vehicle corn oil, concentration 90% w/v); no controls; feeding *ad libitum* (food was withheld 16 hrs prior to dosing).
	Observations	Mortality several times on day 1 and daily thereafter until day 14. Clinical signs several times on day 1 and daily thereafter until day 14. Necropsy on day 14.

Results

Dose [mg/kg bw]\effect		39800	
Sex	**Day**	M	F
Mortality	1-14	None	
Clinical signs[A]	1-14	+	+
Necropsy[B]	14	+	+

(A) Clinical observations included depression, decreased respiration, messy fur and diarrhoea during the first 72 hours.
(B) Findings consisted of focal haemorrhage and congestion (diffuse and focal) of the lungs, congested adrenals and enlarged heart, congested mucosa of the stomach, hydrophenosis and congested medulla of the kidneys and soft heart.

Conclusions Oral LD_{50} > 39800 mg/kg bw.
Rev. note 1. No measurements for body weights were performed during the study.
2. Information about several aspects was incomplete.
Klimisch criterium 2 Limited report. Non-GLP study.

4.35
Title **CAS:** 8007-43-o: acute oral toxicity study in male and female rats
Date of report December 1, 1966.
GLP No.
Test substance CAS: 8007-43-0, purity: not indicated.
Guideline Not indicated.
Stat. method Not indicated.
Test system
Species Rat (Wistar), weight males 133 — 148 g, females 145 · 162 g.
No. of animals 1 O/sex/treatment.
Dosage Single oral administration of 39800 mg/kg bw (vehicle corn oil, concentration 90% w/v); no controls; feeding ad *libitum* (food was withheld 16 hrs prior to dosing).
Observations Mortality several times on day 1 and daily thereafter until day 14.
Clinical signs several times on day 1 and daily thereafter until day 14.
Necropsy on day 14.

Results

Dose [mg/kg bw]\effect		39800	
Sex	Day	M	F
Mortality	I-14	None	
Clinical signs[A]	1-14	i-	+
Necropsy[B]	14	+	+

(A) Clinical observations included depression, decreased respiration, messy fur and diarrhoea during the first 5 days.
(B) Findings consisted of oedema of the lungs, congestion of the adrenals, pelvic dilation, bladder filled with fluid and slight congestion of the stomach mucosa, consolidation of lungs, congestion of the lungs and medullaty congestion in the kidneys.

Conclusions Oral LD_{50} > 39800 mg/kg bw.
Rev. note No body weight measurements were performed during the study.
Klimisch criterium 2 Limited report. Non-GLP study.

GROUP E

4.36
Title **CAS:** 67762-53-2; 67762-52-l : Acute oral toxicity study in rats
Date of report March 26, 1999.
GLP **Yes.**
Test substance CAS: 67762-53-2 and 67762-52-1, purity 100% (81% 67762-53-2 and 19% 67762-52-l).
Guideline OECD 420.
Stat. method Not required.
Test system
Species Rat (Sprague-Dawley Crl:CD), weight males 287-349 g, females 216-236 g, 9-12 weeks old.
No. of animals 5/sex/treatment.
Dosage Single oral administration (gavage) of 1940 mg/kg (dose volume 2.0 ml/kg); no controls; feeding ad *libitum* (food was withheld -18 h prior to dosing and -4 h after dosing).
Observations Mortality twice daily for 14 days.
Clinical signs several times on day 1 and daily until day 15.
Body weights on day 1, 8 and 15.
Necropsy on day 15.

Results

Dose [g/kg bw]\effect		2.0	
Sex	Day	M	F
Mortality	1-15	None	
Clinical signs[A]	1-15	No treatment related effects	
Body weight gain	1-15	No treatment related effects	
Necropsy	15	No effects	

(A) One male animal had unformed stool 4 hours after administration.

Conclusions Oral LD_{50} > 1940 mg/kg bw.
Rev. note *Minor remark.* The actual amount of test material administered was 1.94 g/kg rather than 2.0 g/kg.
Klimisch criterium 1

4.37
Title Acute oral toxicity study with **CAS: 11138-60-6** in rats.
Date of report January 21, 1997.
GLP **Yes.**
Test substance CAS: 11138-60-6, purity not indicated.
Guideline OECD 401.
Stat. method Not required.
Test system
Species Rat (Sprague-Dawley), weight of males 302-306 g, females 208-216 g.
No. of animals 5/sex/treatment.
Dosage Single oral (gavage) administration of 5000 mg/kg (dosing volume 5.3 ml/kg): no controls; feeding ad *libitum* (food was withheld -18 h prior to dosing and -4 h after dosing).
Observations Mortality twice daily until day 15.
Clinical signs three times on day 1 and daily until day 15.
Body weights on day 0, 1, 8 and 15.
Necropsy on day 15.

Results

Dose [mg/kg bw] \ effect	5000	
Sex	tvl	F
Mortality/Clinical signs[A]	None	
Body weight gain	No treatment related effects	
Necropsy	No abnormalities	

(A) Due to a technician error, females were not examined on day 3 and males not on day 5; however, they were observed for viability in the morning and afternoon and were free of significant toxicological signs.

Conclusions Oral LD_{50} > 5000 mg/kg.
Klimisch criterium 1

4.38
Title Acute oral toxicity study
Date of report November 2, 1973.
GLP **No.**
Test substance CAS: 126-57-8, purity not indicated.
Guideline Not indicated.
Stat. method Not applicable.
Test system
Species Rat (Sherman-Wistar).
No. of animals 5/sex/treatment.
Dosage Single oral (gavage) administration of 5.0 g/kg; no controls; feeding ad *libitum* (food was withheld -24 h prior to dosing).
Observations Mortality/clinical signs for 14 days.

Results

Dose [g/kg bw] \ effect	5.0	
Sex	M	F
Mortality	None	

Conclusions Oral LD_{50} > 5.0 g/kg.
Rev. note The report was limited. No report was made on clinical signs and neither measurements of body weights nor necropsy were performed.
Klimisch criterium 2 Limited report, non-GLP

4.39
Title Acute Oral Toxicity Study of CAS: 126-57-8 in Rats
Date of report June 12, 1997.
GLP Yes.
Test substance CAS: 126-57-8, purity 100% (MSDS).
Guideline OECD 401.
Stat. method Not applicable.
Test system
Species Rat (Crl:CD), weight 238-261 g.
No. of animals 5/sex/treatment.
Dosage Single oral administration (gavage) of 2000 mg/kg bw (dosing volume 2.17 ml/kg bw); no controls; feeding *ad libitum* (food was withheld -17 - 20 h prior to dosing).
Observations Mortality twice daily until day 13 and once on day 14.
Clinical signs several times on day 0 and daily until day 14.
Body weights on day 0, 7 and 14.
Necropsy on day 14.

Results

Dose [mg/kg bw]\effect		2000	
Sex	Day	M	F
Mortality	o-14	None	
Clinical signs	o-14	No treatment related effects	
Body weight gain	o-14	No treatment related effects	
Necropsy	14	No treatment related effects	

Conclusions Oral LD_{50} > 2000 mg/kg bw.
Klimisch criterium 1

4.40
Title Single dose oral toxicity study in rats
Date of report September 13, 1982.
GLP No.
Test substance CAS: 70983-72-I) purity: not indicated.
Guideline Not indicated.
Stat. method Not applicable.
Test system
Species Rat (Wistar), weight 200-224 g.
No. of animals 10 males/treatment.
Dosage Single oral administration (gavage) of 5000 mg/kg bw (dosing volume 0.97 — 1 .O ml); no controls; feeding *ad libitum* (food was withheld -16 - 20 h prior to dosing).
Observations Mortality 3 - 4 hours post dosing and daily thereafter until day 14.
Clinical signs 3 - 4 hours post dosing and daily thereafter until day 14.
Body weights on day 0 and 14.
Necropsy on day 14.

Results

Dose [mg/kg bw]\effect		5000
Sex	**Day**	**M**
Mortality	o-14	None
Clinical signs[(A)]	o-14	No treatment related effects
Body weight	o-14	No treatment related effects
Necropsy	14	No treatment related effects

(A) Clinical observations included chromodacryorrhea, piloerection, anogenital area wet or stained yellow and respiratory rattle during one day.

Conclusions Oral LD_{50} > 5000 mg/kg bw.

Rev. note
1. Only males are used in this test.
2. No measurements for body weights were performed on day 7.

Klimisch criterium 2 Limited report. Non-GLP study.

4.41

Title Single dose oral toxicity in rats.

Date of report September 9, 1982.

GLP No.

Test substance CAS: 68424-34-0, purity not indicated.

Guideline Not indicated.

Stat. method Not applicable.

Test system

Species Rat (Wistar), weight 200-233 g.

No. of animals 10 males/treatment.

Dosage Single oral (gavage) administration of 5.0 g/kg; no controls; feeding ad *libitum* (food was withheld -16-20 h prior to dosing).

Observations Mortality/clinical signs 3-4 hours post dose and daily until day 14.
Body weights on day 0 and 14.
Necropsy on day 14.

Results

Dose [g/kg bw] \ effect	Day	5.0
Mortality	o-14	None
Clinical signs[(A)]	o-1 4	+
Body weight gain	14	No treatment related effects
Necropsy	14	No treatment related effects

(A) Clinical observations included chromodacryorrhea, ptosis and piloerection.

Conclusions Oral LD_{50} > 5.0 g/kg in male rats.

Rev. note The report was limited. No females were treated and body weights should have been determined every week.

Klimisch criterium 2 Report was limited to the above mentioned.

4.42

Title Acute oral toxicity study of **CAS: 66424-31-7** in the Rats
Date of report November 16, 1987.
GLP Yes.
Test substance CAS: 68424-31-7, purity approximately 100%.
Guideline 84/449/EEC B1.
Stat. method Not indicated.
Test system
Species Rat (Wistar), weight males 205 - 224 g, females 161 - 179 g, age 7 weeks.
No. of animals S/sex/treatment.
Dosage Single oral administration of 5000 mg/kg bw (dosing volume 5.5 ml/kg); no controls; feeding ad *libitum* (food was withheld overnight prior to dosing and -3 - 4 h after dosing).
Observations Mortality / clinical signs several times on day 0 (day of dosing) and daily until day 14.
Body weights on day 0, 7 and 14.
Necropsy on day 14.

Results

Dose [mg/kg bw]\effect		5000	
Sex	**Day**	**M**	**F**
Mortality	o-14	None	
Clinical-signs	0-14	No treatment related effects	
Body weight gain	o-14	No treatment related effects	
Necropsy	14	No treatment related effects	

Conclusions Oral LD_{50} > 5000 mg/kg bw.
Klimisch criterium 1

4.43

Title Acute oral toxicity of **CAS:** 126-57-a to the rat
Date of report March 16, 1988.
GLP **Yes.**
Test substance CAS: 126-57-8, purity: approximately 100%.
Guideline OECD 401, 67/548/EEC Bl.
Stat. method Not applicable.
Test system
Species Rat (Wistar), weight males 284 - 298 g, females 200 - 210 g, 8 weeks old.
No. of animals 5/sex/treatment.
Dosage Single oral administration (gavage) of 2000 mg/kg bw (dosing volume 2.2 ml/kg), no controls; feeding ad *libitum* (food was withheld overnight prior to dosing and -3 h after dosing).
Observations Mortality and clinical signs several times on day of dosing (day 0) and daily until day 14.
Body weights on day 0, 7 and 14.
Necropsy on day 14.

Results

Dose [mg/kg bw]\effect		2000	
Sex	**Day**	**M**	**F**
Mortality	o-14	None	
Clinical signs	0-14	No treatment related effects	
Body weight (gain)	0-14	No treatment related effects	
Necropsy	14	No treatment related effects	

Conclusions Oral LD_{50} > 2000 mg/kg bw.
Klimisch criterium 1

Acute inhalation toxicity

GROUP A

No data available

GROUP B

4.44

Title		Range-finding inhalation toxicity study of **CAS: 16956-92-2**
Date of report		August **14, 1989.**
GLP		No.
Test substance		CAS: 16958-92-2.
Guideline		Not indicated.
Stat. method		ANOVA, Turkey's multiple range test.
Test system	**Species**	Rat (Sprague Dawley), age 11 weeks, mean weight 370 g (males), 255 g (females).
	No. of animals	1 O/sex/dose group.
	Dosage	Whole body exposure at 0, 0.25 and 0.51 mg/l (6 h/day, 5 d/wk) during 2 weeks (total 10 exposures) in a 400 L inhalation chamber; 35-43 air changes/ hour.
	Analyses	. Concentrations gravimetrically at least 3 times daily for exposure groups and once daily for the sham-exposed controls. . Particle size once during exposure using a cascade impactor.
	Observations	Mortality/clinical signs daily before and during exposure. Body weights on days 1, 8 and prior to necropsy. Organ weights of liver, kidneys, thymus, and right-middle lung lobe (wet and dry). Histopathology on nasal turbinates, lung, tracheobronchial lymph nodes, kidneys and any gross lesions.
Results	**Analyses**	Analytical results in table 1; biological results in table 2.

Table 1

Nominal concentration (mg/l)	0	**0.32**	**0.65**
Measured concentration (mg/l)	N/A	0.25±0.02	**0.51** ±0.02
Mean particle size µm	N/A	1.1±0.3	0.9±0.1

Table 2

Dose [mg/L]/effect	**0**		**0.25**		**0.51**		**DR**
Sex	**M**	**F**	**M**	**F**	**M**	**F**	
Mortality	None						
Clinical signs[A]	No treatment related findings						
Body weight	No treatment related findings						
Organ weight[(B)]	No treatment related findings						
Necropsy	No treatment related findings						
Histopathology	No treatment related findings						

(A) The only clinical sign in the top dose was alopecia.
(B) The percent ratio of the dry weight of the right apical lung was low in males and of the middle right high in females at 0.50 mg/l.

Conclusion NOAEL 0.51 mg/l.

Rev. note
1. In comparison with the OECD 412 guideline the following items were not tested or evaluated in this range finding study:
   - An additional dose level or the maximum feasible/ toxic dose level.
   - Food consumption.
   - Haematology and clinical biochemistry parameters.
   - Adrenals and testes not weighed.
   - Histopathology examination of the adrenals, heart and spleen.
2. This study represents a meaningful toxicological evaluation of the inhalation exposure to **CAS: 16958-92-2.** However, for a full toxicological profile on the effects of inhalation an additional top dose level (note 1; based on anticipated human exposure, maximum feasible dose application or toxic response) should be included and additional toxicological parameters (note 2) should be tested.
3. The airflow through the chamber was higher than required by OECD 412. However, the level mentioned in the guideline needs to be considered as a minimal value, since by a large number of air changes the maintenance of the test substance concentration is guaranteed.

Klimisch Criterium 2 Additional dose level and toxicological parameters to be tested (note 3)

4.45

Title Acute inhalation toxicity study of **CAS: 16958-92-2**

Date of report June 23,1989.

GLP No.

Test substance CAS: 16958-92-2, purity 100%.

Guideline Not indicated.

Stat. method ANOVA, Tukey's multiple range test, Duncan's multiple range test.

Test system

Species Rat (Sprague Dawley), 18 weeks old, mean weight 545-571 g (males), 304-318 g (females)

No. of animals 1 O/sex/treatment.

Dosage Whole body exposure for 4 hours in 400 L inhalation chambers to an aerosol, generated by a Laskin nebuliser (12-23 air changes/h) at 0, 0.6 and 3.9 mg/l; interim kill of 5 animals/sex/treatment on day 2.

Analysis Concentration gravimetrically (weight filter/volume of air passed)
Particle size by cascade impactor

Observations Mortality/clinical signs daily (clinical signs not in weekends).
Body weight on day 1, 2, 8 and 16.
Necropsy on day 2 and 16.
Weight of liver, kidney and right middle lung lobe (wet and dry).
Histopathology of lung, nasal turbinates, tracheal lymph nodes, kidney, liver and gross lesions

Results

Analyses Measured concentration 0.5 and 3.2 mg/l; mass median diameter 0.9-1 .1 µm (SD 1.6-l .8 pm).

Dose (mg/l)	0		0.5		3.2		DR	
Sex	M	F	M	F	M	F	M	F
Mortality	None							
Clinical signs	No treatment related effects							
Body weight (gain)	No treatment related effects							
Necropsy	No treatment related effects							
Histopathology	No treatment related effects							

Conclusions Acute 4-h LC_{50} > 3.2 mg/l.

Rev. note
1. No treatment related effects were reported in animals that were killed on day 2.
2. The airflow through the chamber was higher than required by OECD 403. However, the level mentioned in the guideline needs to be considered as a minimal value, since by a large number of air changes the maintenance of the test substance concentration is guaranteed.

Klimisch criterium 2 Non-GLP.

GROUP C

4.46

Title	Acute Inhalation Toxicity **of CAS: mix of** 67989-24-6 **and** 70024-57-6 in rats	
Date of repot-l	February 1977.	
GLP	**No.**	
Test substance	CAS: mix of 67989-24-6 and 70024-57-6 emulsion, purity not indicated.	
Guideline	Federal Register August 12, 1961 et seq. FHSA	
Stat. method	Not required	
Test system	**Species**	Rat (Wistar), weight 180 - 202 g.
	No. of animals	**10** males.
	Dosage	Head-nose only exposure for 4 h to 200 µl/l (mean calculated concentration); 30 air changes/min.
	Observations	Clinical signs continuously during exposure and at frequent intervals for 14 days Body weights on days 0 , 7 and 14. Necropsy on day 14.
Results	**Analyses**	Concentration assessed by calculation: sample weight/airflow x duration of exposure. Particle size not analysed. Nebulizer produced an aerosol with particle size of < 5 microns.

Dose [µl/l]\effect	200
Sex	M
Mortality	None
Clinical signs(A)	+
Body weight gain	No treatment related effects
Necropsy	No treatment related effects

(A) Clinical signs included increased respiratory rate, a medium degree of apathy and symptoms disappeared within 24 h after exposure.

Conclusions	Acute 4-h LC_{50} >200 µl/l.
Rev. note	1. There were no analyses on the actual concentrations (calculations only), particle size, oxygen concentration, temperature and relative humidity in the exposure chambers. This renders the result less reliable but does not invalidate the study. 2. Only males were used. Therefore, the effect on females remained unknown. 3. The density of the test substance is not known, this hampers the determination of the dose (in mg/l, as required per OECD 403) the animals were exposed to. 4. The airflow through the chamber was higher than required by OECD 403. However, the level mentioned in the guideline needs to be considered as a minimal value, since by a large number of air changes the maintenance of the test substance concentration is guaranteed.
Klimisch criterium	2 Insufficient data on test conditions (note 2) available and no evaluation of the effect on females (note 3).

4.47

Title	Acute inhalation toxicity - CAS: 70729-68-g in rats	
Date of report	September 28, 1979.	
GLP	**No.**	
Test substance	CAS: 70729-68-9, purity: 88%, 6% triethylene glycol di-n-heptanoate, 4% mixed ester of tetraethylene glycol with n-heptanoic and 2 methylhexanoic acids, 2% other mixed esters.	
Guideline	Not indicated.	
Stat. method	Not applicable.	
Test system	**Species**	Rat (Wistar), age -60 days, weight 236-298 g.
	No. of animals	6 males/treatment.
	Dosage	Exposure to vapour of the test substance (heated to 230-400°C) for 4 h in 20L chambers at 2.1, 2.3, 5.3, 12.7, 13.7 and 14.2 mg/L; no controls.
	Analyses	Every 30 minutes during treatment: known volume trapped in acetone and analysed by GC/FID.
	Observations	Mortality/clinical signs/body weight on weekdays for 14 days.

Results

Dose [mg/L]\effect	Day	2.1	2.3	5.3	12.7	13.7	14.1	DR
Mortality	o-14	0/6	0/6	0/6	0/6	0/6	6/6	
Clinical signs[(A)]	o-14	+	+	+	+	+	+	
Body weight	o-14	No treatment related effects						

(A) Clinical signs observed during exposure included salivation, preening, red nasal discharge,
(B) lethargy, irregular respiration and no reaction to sound. All deaths occurred during exposure (animals showed salivation, gasping, irregular respiration and convulsions). Post-exposure staining of the perineal and crust around the nose were observed at 12.7 mg/L.

Conclusions No conclusion was drawn.

Rev. note
1. Only males were tested.
2. The air flow rate during exposure was not indicated.
3. The temperature in the exposure chambers was high (up to 28%). This may lead to an increased breathing rate and a concomitant increased uptake of the test substance. Since this may represent a worst case scenario, the validity of the study is not affected.
4. The concentrations in the study were indicated as measured time-weighed average concentrations. The validation of the analytical method was not reported.
5. The report was limited to the above mentioned. No necropsy was performed.
6. Initial weight loss was observed at 12.7 mg/L after 24 h.

Klimisch criterium 2 Limited report, only males tested.

GROUP D

No data available

GROUP E

No data available

Acute dermal toxicity

GROUP A

4.46

Title Final report on the safety assessment of Octyl Palmitate, Cetyl Palmitate and Isopropyl Palmitate

Date of report 1982.

GLP No.

Test substance CAS: 29806-73-3, Octyl palmitate, purity 98.6% (<1.4% palmitic acid).

Guideline Not indicated.

Stat. method Not applicable.

Test system

Species Rabbit.

No. of animals 2/treatment.

Dosage Dermal application to the intact and clipped skin at 0, 3.9, 6.0 or 9.4 ml/kg (↔0.0, 3400, 5200 or 8100 mg/kg) for 24h with a plastic sleeve.

Observations Mortality/clinical signs for two weeks.

Results

Dose [g/kg] \ effect	Day	0.0	3.4	5.2	8.1	DR
Mortality/clinical signs[A]	1-14	None				

(A)The material produced onlv a mild irritation.

Conclusions Oral LD_{50} > 8.1 g/kg.

Rev. note Dose levels were re-calculated by the reviewer based on the density of the test substance (0.86 g/ml).

Klimisch criterium 4 Limited report, secondary literature.

GROUP B

4.49

Title In vivo percutaneous absorption of **CAS: 16958-92-2** in control and **CAS: 16958-92-2**-treated Sprague Dawley rats

Date of report January 13, 1986.

GLP No.

Test substance CAS: 16958-92-2; ^{14}C-di-tridecyl adipate, Spec. Act. 10 mCi/mmol, radiochemical purity >97% (LCS).

Guideline Not indicated.

Stat. method Not indicated.

Test system

Species Rat (Sprague Dawley), 19.520 weeks old.

No. of animals 4 controls/sex and 5 high dose animals/sex.

Dosage Single dermal application at 2000 mg/kg bw (no vehicle) on the clipped dorsal skin.

Procedures

- The test substance was synthetised by esterification of adipic acid (180 mg cold and 0.9 mg ^{14}C) and tridecyl alcohol (626.5 mg). The dosing solution consisted of a 1:5.5 ratio of ^{14}C-**CAS:** 16958-92-2 and ^{12}C-**CAS: 16958-92-2.**
- The animals were control or high dose (2000 mg/kg bw) animals from a 13 week dermal study (treated parallel to the animals in this study (ref.70)). After this period they were treated topically with ^{14}C-dosing solution (area 1.3 cm^2, covered with gauze mesh) and placed in metabolism cages. Urine and faeces were collected daily over a 4 day period. At termination the amount of radioactivity in urine, faeces (daily samples), liver, kidney, stomach, bladder, small intestine and blood was determined by LCS.

Results Presented as percentage of applied radioactivity.

Dose (mg/kg bw)	0		2000	
Sex	M	F	M	F
Percentage radioactivity recovered	11.6	10.6	10.8	9.1
Urine	3.5	4.7	0.7	1.3
Faeces	0.7	0.4	0.6	0.4
Tissues	7.4	5.5	9.4	7.4

Conclusions Total absorption 9-l 2% (irrespective of pre-treatment); slow elimination from body tissues.

Rev. note
1. The mass balance for the absorption study was only 10%. No report was made on the amount of radio activity that was present in the skin at termination. No metabolites were identified.
2. After 4 days 52-63% (controls) and 81-87% (pre-treated) of the absorbed dose was found in the body tissues.
3. Limited report.

Klimisch criterium 2 Limited report (note 3), mass balance 10% (note 1).

4.50

Title Acute dermal toxicity study.
Date of report December 11, 1973.
GLP No.
Test substance CAS: 16958-92-2, purity not indicated.
Guideline 16 CFR 1500.40.
Stat. method Not applicable.
Test system
Species Rabbit.
No. of animals 3 animals.
Dosage Dermal application at 2.0 g/kg bw.
Observations Mortality daily for 14 days.

Results

Dose [g/kg bw]\effect	Day	2.0
Mortality	o-14	None

Conclusions Dermal LD_{50} > 2.0 g/kg.

Rev. note
1. The sex and age of the animals were not indicated.
2. Only 3 animals were used instead of 10 (five of each sex).
3. No measurements for body weights or clinical examination were performed.
4. No necropsy was performed.

Klimisch criterium 3 The report was limited to the above mentioned, non-GLP.

4.51

Title Acute dermal toxicity in rabbits
Date of report December 4, 1978.
GLP No.
Test substance CAS: 16958-92-2, purity not indicated.
Guideline Not indicated.
Stat. method Not applicable.
Test system
Species Rabbit (New Zealand White), weight 1.9-2.5 kg.
No. of animals 10 animals.
Dosage Dermal application to the abraded skin at 5.0 g/kg bw (no vehicle under semi-occlusive dressing for 24 h); no controls.
Observations Mortality/clinical signs daily for 14 days.
Body weights on day 0 and 14.

Results

Dose [g/kg bw]\effect	Day	5.0
Mortality	o-14	None
Clinical signs[(A)]	o-14	+
Body weight gain	o-14	Treatment related effects

(A)Findings consisted of erythema, oedema, diarrhoea, emaciation, lethargy and bloated abdomen.

Conclusions Dermal LD_{50} > 5.0 g/kg.

Rev. note
1. The test was performed on abraded skin. Since OECD 402 requires a test on intact skin, the results of this study are considered to be not assignable.
2. The sex and age of the animals were not indicated.
3. No measurements for body weights were performed on day 7.
4. No necropsy was performed.

Klimisch criterium 4 Test on abraded skin (note 1).

4.52

Title Range finding toxicity tests.

Date of report January 12, 1977.

GLP No.

Test substance CAS: 142-16-5, di-2-ethylhexyl maleate, purity 100%.

Guideline Not indicated.

Stat. method Not applicable.

Test system

Species Rabbit, mean weight 2306 g.

No. of animals 5 males.

Dosage Dermal application to the clipped skin at 10.0 ml/kg for 24h under polyethylene sheeting; no controls.

Observations Mortality/clinical signs twice on day 1, daily from day 2 to 8, and on day 14.
Body weights on day 1 and 14.
Necropsy on day 14.

Results

Dose [ml/kg bw] \ effect	Day	10.0
Mortality/clinical signs	1-14	None
Body weight gain	I-14	No treatment related effects
Necropsy[(A)]	14	+

(A) Findings consisted of congested spleens, mottled kidneys, opaque intestine.

Conclusions Dermal LD_{50} > 10.0 ml/kg.

Rev. note
1. Dose level (g/kg) could not be calculated, since density was not indicated.
2. 5 males were used instead of 5/sex/dose group.
3. *Minor remarks. No* measurements for body weight on day 7 were performed. The size of the application area was not indicated. It is not clear whether the dressing used was occlusive.

Klimisch criterium 2 Report was limited to the above mentioned, non-GLP.

GROUP C

No data available.

GROUP D

4.53

Title	Final report on the safety assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate
Date of report	1985.
GLP	No.
Test substance	CAS: 8007-43-0, Sorbitan sesquioleate, purity not indicated.
Guideline	Not indicated.
Stat. method	Not applicable.
Test system	**Species** Rabbit.
	No. of animals 2/sex/treatment.
	Dosage Dermal exposure of 24 hours to 6.8 g/kg or 10.2 g/kg (3%) ↔ 0.2 g/kg or 0.3 g/kg; no controls.
	Observations Mortality/clinical signs/behaviour/body weight changes/gross alterations for 14 days.

Results

Dose [g/kg bw] \ effect		0.2		0.3		DR	
Sex	Day	M	F	M	F	M	F
Mortality	1-14	None					
Clinical signs/ behaviour(A)	I-14	No treatment related effects					
Body weight	1-14	No treatment related effects					
Necropsy	15	No treatment related effects					

(A) Erythema at the contact site was seen on each animal.

Conclusions	Dermal LD_{50} > 0.3 g/kg bw.
Klimisch criterium	4 Limited report, secondary literature.

4.54

Title	Final report on the safety assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate
Date of report	1985.
GLP	No.
Test substance	CAS: 8007-43-0, Sorbitan sesquioleate, purity not indicated.
Guideline	Not indicated.
Stat. method	Not applicable.
Test system	**Species** Rabbit.
	No. of animals 2/sex/treatment.
	Dosage Dermal exposure of 24 hours to 6.8 g/kg or 10.2 g/kg (3%) ↔ 0.2 g/kg or 0.3 g/kg; no controls.
	Observations Mortality/clinical signs/behaviour/body weight changes/gross alterations for 14 days.

Results

Dose [g/kg bw] \ effect		0.2		0.3		DR	
Sex	Day	M	F	M	F	M	F
Mortality	1-14	None					
Clinical signs/ behaviour(A)	I-14	No treatment related effects					
Body weight	1-14	No treatment related effects					
Necropsy	15	No treatment related effects					

(A) Erythema at the contact site was seen on each animal.

Conclusions	Dermal LD_{50} > 0.3 g/kg bw.
Klimisch criterium	4 Limited report, secondary literature.

GROUP E

4.55

Title Acute dermal toxicity study with **CAS: 11138-60-6** in rabbits
Date of report January 21, 1997.
GLP Yes.
Test substance CAS: 11138-60-6, purity: not indicated.
Guideline OECD 402.
Stat. method Not applicable.
Test system
Species Rabbit (New Zealand White), age ~ 8 weeks, weight males 2.4-3.1 kg, females 2.5-2.7 kg.
No. of animals 5/sex/treatment.
Dosage Dermal application to the clipped skin (12 x 14 cm) at 2000 mg/kg bw (no vehicle under semi-occlusive dressing for 24 h); no controls; feeding at fixed rate (125 g/day).
Observations Mortality twice daily until day 15.
Clinical signs several times on day 1 and daily until day 15.
Body weights on day 1, 8 and 15.
Necropsy on day 15.

Results

Dose [mg/kg bw]\effect		2000	
Sex	Day	M	F
Mortality	1-15	None	
Clinical signs	I-15	No treatment related effects	
Body weight (gain)	1-15	d	
Necropsy	15	No treatment related effects	

Conclusions Dermal LD_{50} > 2000 mg/kg bw.
Rev. note Body weight of one male was decreased on day 8 (0.4 kg) and 15 (0.3 kg) compared to day 0. This effect is commonly seen in this type of study and probably due to discomfort of the bandage. In three other males slight body weight loss was reported on day 15. Since this effect was very marginal, it was considered not to be related to treatment with the test substance.
Klimisch criterium 1

4.56

Title Acute dermal toxicity study.
Date of report November 6, 1973.
GLP No.
Test substance CAS: 126-57-8, purity not indicated.
Guideline 16 CFR 1500.40.
Stat. method Not applicable.
Test system
Species Rabbit.
No. of animals 3 animals.
Dosage Dermal application at 2.0 g/kg bw.
Observations Mortality daily for 14 days.

Results

Dose [g/kg bw]\effect	Day	2.0
Mortality	o-14	None

Conclusions Dermal LD_{50} > 2.0 g/kg.
Rev. note
1. The sex and age of the animals were not indicated.
2. Only 3 animals were used instead of 10 (five of each sex).
3. No measurements for body weights or clinical examination were performed.
4. No necropsy was performed.

Klimisch criterium 3 The report was limited to the above mentioned, non-GLP.

Genetic toxicity in vivo

GROUP A

No data available.

GROUP B

4.57

Title	Micronucleus assay of bone marrow and peripheral red blood cells in rats treated via dermal administration of **CAS: 16958-92-2**
Date of report	February 5, 1986.
GLP	**No.**
Test substance	CAS: 16958-92-2; di-tridecyl adipate, purity 100%.
Guideline	Not indicated.
Stat. method	ANOVA, Tukey's test, Sheffe's test, linear regression.
Test system	**Species** Rat (Sprague Dawley), 6.5-7 weeks old.
	No. of animals 1 O/sex/dose level.
	Dosage Dermal administration for 13 weeks (5 days/week) at 0, 800 and 2000 mg/kg bw (no vehicle) on the clipped dorsal skin; untreated controls.
	Sampling time At necropsy.
	Pos. control Not included.
	Scoring For each animal (study ref. 70), the following proportions were determined in bone marrow (4 smears/animal) and peripheral blood (3 slides/animal): Ratio PolyChromatic Erythrocytes (PCE) and NormoChromatic Erythrocytes (NCE). Micronucleated PolyChromatic Erythrocytes (MPCE) per 1000 PCE. Micronucleated NormoChromatic Erythrocytes (MNCE) per 1000 NCE.

Results

Dose [mg a.i./kg bw]/effect	*0*	800	2000
Mortality	None		
Clinical signs(A)	Not reported		
Bone marrow			
PCE/NCE	no treatment related effects		
MNCE [% of PCE]	no treatment related effects		
MPCE [% of PCE]	no treatment related effects		
Peripheral blood			
PCE/NCE	no treatment related effects		
MNCE [% of PCE]	no treatment related effects		
MPCE [% of PCE]	no treatment related effects		

(A) See ref. 70

Conclusion	Not clastogenic.
Rev. note	1. Due to the use of animals from a 13-week dermal toxicity study it was not possible to include positive controls, as is required by OECD 474. The interval between the last dosing time and the collection of blood and bone marrow is not indicated.
	2. The high dose was above the 1000 mg/kg indicated as a maximum dose by the guideline. However, since absorption was about 10% (see ref.70), the internal dose was well below this maximum (i.e. 1000).
	3. *Minor remarks* The proportion of MPCE was determined for 1000 PCE. This is in agreement with OECD 474 (1983); OECD 474 (1997) requires evaluation of 2000 PCE.
Klimisch Criterium	1

Genetic toxicity in vitro

GROUP A

No data available.

GROUP B

4.59

Title	Mutagenicity testing of di(2-ethylhexyl)phthalate and related chemicals in *Salmonella*	
Date of report	1984.	
GLP	No.	
Test substance	CAS: 122-62-3, di(2-ethylhexyl)sebacate, purity not indicated.	
Guideline	Not indicated.	
Test system	**Bacterial strains**	**TA98, TA1 00, TA1535, TA1537.**
	Metabolic activation	Rat/hamster liver S9 mix (Aroclor 1254-induced).
	Test concentration	100, 333, 1000, 3333, 10000 µg/plate.
	Controls	Neaative: vehicle (DMSO). Positive: 2-aminoanthracene (all strains with S9); 4-nitro-o-phenylenediamine (TA98), sodium azide (TA1 00, TA1535), 9-aminoacridine (TA1537) (all without S9).
	Procedure	According to OECD 471.

Results

Tester strain	Test result (A)	
	Without activation	With activation
TA98		
TA100		
TA1535		
TA1537		

(A) +/- ; oositivelnegative result; positive controls gave expected responses.

Conclusion Not mutagenic.

Rev. note
1. Precipitate was observed at 3333 and 10000 µg/plate in the assay with 1535. No appreciable toxicity was observed.
2. Only four strains of Salmonella were used and no triplicate plating was used.

Klimisch criterium 2 Non-GLP study.

4.60

Title Mutagenicity evaluation of **CAS: 16958-92-2** in the Ames *Salmonella/Microsome* plate test

Date of report May 1, 1978.

GLP No.

Test substance CAS: 16958-92-2, purity: not indicated.

Guideline Not indicated.

Test system

Bacterial strains	TA98, TA100, TA1535, TA1537, TA1538.
Metabolic activation	Rat liver S9 mix (Aroclor-induced).
Test concentration	0.01, 0.10, 1, 5 and 10 µl/plate.
Controls	Neoative: vehicle (DMSO). Positive: ethylmethanesulfonate (TA1535, TA100), QM (TA1537), nitrofluorene (TA1538, TA98), all strains without S9; aminoanthracene, all strains with S9.
Procedure	According to OECD 471.

Results

Tester strain	Test result (A)	
	Without activation	With activation
TA98		
TA100		
TA1535		
TA1537		
TA1538		

(A) +/- : positive/negative result; positive controls gave expected responses.

Conclusion Not mutagenic.

Rev. note
1. Plating was not done in duplicate or triplicate, but once.
2. It is not mentioned if precipitation **was** found at any of the tested concentrations.

Klimisch criterium **2**

GROUP C

4.61

Title Mutagenic activity in the *Salmonella*/microsome assay
Date of report December 20, 1979.
GLP No.
Test substance CAS: 70729-68-9, purity: 88%, 6% triethylene glycol di-n-heptanoate, 4% mixed ester of tetraethylene glycol with n-heptanoic and 2 methylhexanoic acids, 2% other mixed esters.
Guideline Not indicated.
Stat. method Z-test based on Poisson distribution.
Test system
- **Bacterial strains** TA98, TA100, TA1535 and TA1537.
- **Metabolic activation** Rat liver S9 (Aroclor 1254 induced).
- **Test concentration** 500-10,000 µg/plate, 100-2500 µg/plate (based on toxicity with TA1535).
- **Controls** Negative : DMSO (vehicle)
  Positive: N-methyl-N'-nitro-N-nitroguanidine (TA100 and TA1535 without S9), 9-aminoacridine (TA1537 without S9), 2-nitrofluorene (TA98 without S9) and 2-aminoanthracene (all strains with S9).
- **Procedure** Plate incorporation test according to OECD 471 with independent repeat.

Results

Tester strain	Test result (A)	
	Without activation	With activation
TA98		
TA100		
TA1535		
TA1537		

(A) +/- : positive/negative result; positive controls gave expected responses.

Conclusions Negative.
Rev. note
1. Only 2 replicates were plated per test.
2. OECD 471 requires that 5 different strains are tested.

Klimisch criterium 1

4.62

Title Chinese hamster ovary cell assay for mutagenicity
Date of report June 25, 1981.
GLP No.
Test substance CAS: 70729-68-9, purity: 88%, 6% triethylene glycol di-n-heptanoate, 4% mixed ester of tetraethylene glycol with n-heptanoic and 2 methylhexanoic acids, 2% other mixed esters.
Guideline Not indicated.
Stat. method Student's t-test, ANOVA.
Test system
- **Cell line** CHO-cells (BH4 clone)
- **Metabolic activation** Rat S9 mix (Aroclor 1254 induced).
- **Test concentrations** -S9: 0.27-23.9 mM, based on solubility; vehicle DMSO
  +S9: 0.25-23.9 mM, based on solubility; vehicle DMSO.
- **Controls** Neaative: vehicle controls.
  Positive: ethylmethane-sulfonate (-S9), 7,12-dimethylbenzanthracene (+S9).
- **Procedure** Three independent tests; duplicate cultures/treatment; no. of cells 1 0^6 ; exposure period 18-19 hours (-S9) and 5 hours (+S9); expression period 7 days; endpoint: forward mutation on HGPRT locus.

Results

Test no.	Metabolic activation	Doses tested [mM]	Cytotoxicity [% of control survival] at highest dose	Test result(A)
1	Without	0.27, 1.2, 2.7, 5.5, 13.6, 23.9	100	
	With	0.25, 1.2, 2.5, 7.5, 16.0, 23.9	96	
2	Without	0.27, 1.2, 2.7, 5.5, 13.6, 23.9	83	
	With	0.25, 1.2, 2.5, 7.5, 16.0, 23.9	75	
3	Without	0.27, 2.7, 13.6, 23.9	88	
	With	0.25, 1.2, 2.5, 7.5, 16.0, 23.9	99	

(A)+/- : positive/negative result; positive controls gave expected responses.

Conclusion Not mutagenic.

Rev. note
1. It is not clear from the description of the results at which concentrations precipitate was observed.
2. *Minor remark No* individual data were presented.

Klimisch criterium 1

GROUP D

4.63

Title Final report on the safety assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate

Date of report 1965.

GLP No.

Test substance CAS: 1338-41-6, Sorbitan stearate, purity not indicated.

Guideline Not indicated.

	Ames	SHE
Result	negative	negative

Conclusions Not mutagenic

Klimisch criterium 4 Limited report, secondary literature.

9.4.64

Title Studies of *in* vitro cell transformation and mutagenicity by surfactants and other compounds.

Date of report 1980.

GLP No.

Test substance CAS: 1336-41-6, purity not indicated.

Guideline Not indicated

Stat. method Not indicated.

Results

Test	Range of test concentrations	Metabolic activation	Result (A)
Ames (TA98 and TA 100)	1 O-2000 μg/plate	-S9 +S9	
Cell transformation (Hamster embryo cells)	I-300 μg/ml 1 O-1 00 μg/ml		

(A) +/- : positive/negative result.

Rev. note
1. For the transformation test no reference was made to the use of metabolic activation.
2. Journal article.

Klimisch criterium 3 Secondary literature (note 2)

GROUP E

4.65

Title	Mutagenicity test with **CAS: 67762-53-2 and** *67762-52-l* in the *Salmonella* - *Escherichia* Co/i/mammalian - microsome reverse mutation assay	
Date of repot-l	February 2, 1999.	
GLP	Yes.	
Test substance	CAS: 67762-53-2 and 67762-52-i) purity 100% (61% 67762-53-2 and 19% 67762-52-1).	
Guideline	Not indicated.	
Test system	**Bacterial strains**	TA98, TA100, TA1535, TA1537, WP2 uvrA.
	Metabolic activation	Rat liver S9 mix (Aroclor 1254-induced).
	Test concentration	33.3, 100, 333, 1000, 3330, 5000 μg/plate.
	Controls	Neaative: vehicle (ethanol). Positive: 2-aminoanthracene (TA1 00, TA1535, TA1537, Wp2uvrA), benzo(a)pyrene (TA98), all with S9; sodium azide (TA100, TA1535), 2-nitrofluorene (TA98), 4-nitroquinoline-N-oxide (WP2 uvrA), ICR-191 (TA1537), all without S9.
	Procedure	According to OECD 471.

Results

	Test result (A)	
Tester strain	**Without activation**	**With activation**
TA98		
TA100		
TA1535		
TA1537		
TA1538		
WP2 uvrA		

(A) +/- : positive/negative result; positive controls gave expected responses.

Conclusion	Not mutagenic.
Rev. note	Precipitate was observed at 333 to 5000 μg/plate. No appreciable toxicity was observed.
Klimisch criterium	1

4.66

Title	Bacterial Reverse Mutation Assay with an Independent Repeat Assay	
Date of report	August 29, 1996.	
GLP	Yes.	
Test substance	CAS: 11138-60-6, purity: not indicated.	
Guideline	Not indicated.	
Test system	**Bacterial strains**	TA98, TA100, TA1535, TA1537, TA1538), WP2 uvrA.
	Metabolic activation	Rat liver S9 mix (Aroclor 1254-induced).
	Test concentration	10, 33, 100, 333, 1000 μg/plate (without S9) 33, 100,333, 1000, 5000 μg/plate (with S9).
	Controls	Neaative: vehicle (ethanol). Positive: 2-aminoanthracene (all strains with S9); 2-nitrofluorene (TA98, TA1538), sodium azide (TA100, TA1535, 9-aminoacridine (TA1537), methyl methanesulfonate (WP2 uvrA) (all without S9).
	Procedure	According to OECD 471.

Results

Tester strain	Test result (A)	
	Without activation	With activation
TA98		
TA100		
TA1535		
TA1537		
TA1538		

(A) +/- : positive/negative result; positive controls gave expected responses.

Conclusion Not mutagenic.

Rev. note Precipitate was observed at ≥100 to 5000 μg/plate. No appreciable toxicity was observed.

Klimisch criterium 1

4.67

Title In vitro mammalian chromosome aberration test

Date of report October 28, 1996.

GLP Yes.

Test substance CAS: 11138-60-6, purity not indicated.

Guideline Not indicated.

Stat. method Fisher 's exact test, Cochran-Armitage test.

Test system

Cell line CHO cells.

Metabolic activation Rat S9 mix (Aroclor 1254-induced).

Test concentrations 625, 1250, 2500 and 5000 μg/ml, based on limited toxicity.

Controls Neaative: vehicle controls (ethanol).
Positive: mitomycin-C (-S9), cyclophosphamide (+S9).

Procedure -S9: 4 h exposure + 16 h recovery.
20 h exposure.
+S9: 4 h exposure + 16 h recovery.
Colcemid was added for the last 2 hours.

Results

Exposure (h)	Metabolic activation	Doses tested [μg/ml]	Aberrations [%]	Test result(A)
4	Without	625, 1250, 2500, 5000	0, 2, 2, 0	
	With	625, 1250, 2500, 5000	2, 3.5, 2, 1	
20	Without	625, 1250, 2500, 5000	1, 2, 2.5, 1.5	

(A)+/- : positive/negative result; positive controls gave expected responses.

Conclusion Not clastogenic.

Rev. note The test without metabolic activation was performed twice, but only the results of the second test were presented.

Klimisch criterium 1

4.68

Title Mutagenicity test with **CAS: 126-57-8** in the Salmonella - *Escherichia Coli*/mammalian-microsome reverse mutation assay with a confirmatory assay

Date of report June 23, 1997.

GLP Yes.

Test substance CAS: 126-57-8, purity 100% (MSDS).

Guideline Not indicated.

Test system

Bacterial strains TA98, TAIOO, TA1535, TA1537, WP2uvrA.

Metabolic activation Rat liver S9 mix (Aroclor 1254-induced).

Test concentration 100, 333, 1000, 3330 and 5000 μg/plate.

Controls Neaative: vehicle (DMF).
Positive: 2-aminoanthracene (all strains with S9); sodium azide (TAIOO, TA1535), 2-nitrofluorene (TA98), ICR-191 (TA1537), 4-nitroquinoline-N-oxide (WP2uvrA), all without S9.

Procedure According to OECD 471.

Results

	Test result [A]	
Tester strain	**Without activation**	**With activation**
TA98		
TA100		
TA1535		
TA1537		
WP2uvrA		

(A) +/- : positive/negative result; positive controls gave expected responses.

Conclusion Not mutagenic.

Rev. note Precipitation (slight) was observed at 333 µg/plate and above. This means that the test concentrations were too high. However this does not affect the validity of the test since no effect was seen.

Klimisch criterium 1

Repeated dose toxicity

GROUP A

4.70

Title Final report on the safety assessment of Octyl Palmitate, Cetyl Palmitate and Isopropyl Palmitate

Date of report 1982.

GLP No.

Test substance CAS: 29806-73-3, Octyl palmitate, purity 98.6% (<1.4% palmitic acid).

Guideline Not indicated.

Stat. method Not applicable.

Test system

Species	rat	rabbit
No. animals	1 O/sex/treatment	3
Dosage	Applications of 1 .O ml/kg (0.86 g/kg) to the shaved skin 5 days/week total of 27 applications during six weeks.	Daily application for 60 days. A 5 cm^2 area remained untreated and served as control.
Observations	Clinical signs and mortality daily. At termination complete gross necropsy, histopathology, and blood tests.	Mortality, clinical signs and histological examination.
Results	Mean hematocrit and red blood cell values of male rats were significantly lower compared to controls. No clinical signs or mortality.	The ingredient was poorly tolerated and congestive dermatitis was observed. No mortality.

Conclusions No systemic toxic effects.

Rev. note
1. No adequate control was included in the study with rabbits. An untreated area of the skin can only be used as control for local (skin) effects.
2. Dose levels were re-calculated by the reviewer based on the density of the test substance (0.86 g/ml).

Klimisch criterium 4 Limited report, secondary literature.

GROUP B

4.72

Title Thirteen-week dermal administration of CAS: 16958-92-2 (CAS: 16958-92-2) to rats

Date of report April 6, 1988.

GLP No.

Test substance CAS: 16958-92-2; di-tridecyl adipate, purity not indicated.

Guideline Not indicated.

Stat. method Dunnett's test, Duncan's Multiple Range test, chi-square distribution.

Test system

Species Rat (Sprague Dawley), 6.5-7 weeks old.

No. of animals 1 O/sex/dose level; additionally 5 control and 5 high dose animals for percutaneous absorption study.

Dosage Dermal administration for 13 weeks (5 days/week) at 0, 800 and 2000 mg/kg bw (no vehicle) on the clipped dorsal skin; untreated controls.

Observations

- Mainly as required by OECD 411 (no food consumption and ophthalmoscopy); in 5 high dose and 5 control males weight and histopathology of the epididymides and sperm analysis.
- After 13 weeks the additional control and high dose animals were treated with ^{14}C-test substance (area 1.3 cm^2, covered with gauze mesh) and placed in metabolism cages, urine and faeces were collected over a 4 day period. At termination the amount of radioactivity in urine, faeces and tissues and organs was determined by LCS.

Results Radioactivity recove d: 9-12% of applied details in ref 66 .

Dose mg/kg bw)	0		800		2000		DR	
Sex	M	F	M	F	M	F	M	F
Mortality	1/20		0/10	0/10	0/10	0/10		
Clinical signs			Not reported					
rritation (A)			+	+	+	+		
3ody weight			d	d	d	d		
iaematology			No treatment related effects					
Clinical biochemistry								
ALAT			I		I			
ALP			ic		ic			
Glucose			dc	dc	dc	dc	x	
Urinalysis (B)			No treatment related effects					
Sperm morphology			No treatment related effects					
Organ weight								
Kidney			ic^r	ic^r	ic^r	ic^r	x	x
Liver			ic^r	ic^r	ic^r	ic^r	x	x
Adrenals						ic^r		
Heart						ic'		
Epididymides					ic'			
Thyroid					ic'			
Uterus						ic^r		
Necropsy			No treatment related effects					
Histopathology (C)			nd	nd	+	+		

nd = not determined.

(A) Slight erythema and flaking of the skin.

(B) Slight increase in protein and ketone bodies in treated animals.

(C) Hyperplasia of sebaceous glands (males + females) and cysts and pelvic dilatation in the kidney (females only).

Conclusions NOAEL < 800 mg/kg bw.

Rev. note

1. The effects on organ weights for liver and kidney was considered to be related to the applied dose.
2. The test substance is not sufficiently identified.
3. The author of the report concluded that no systemic toxicity was seen at any of the doses (NOAEL 2000 mg/kg bw). According to the reviewer the effects on body weight, liver and kidney weight and on liver enzymes are related to treatment.
4. The application area was not indicated and may have been larger than 10% of the total body surface area. Since animals wore collars to prevent oral ingestion of the test substance, the test site was left uncovered (OECD 411 indicated a porous dressing to be applied), which may influence absorption.
5. Only 2 dose levels were tested and no report is made on clinical observations. No individual data were presented on any of the endpoints measured. Therefore proper evaluation is hampered.

Klimisch criterium 2 Limited report (note 4), inappropriate application (note 3) and no identity of the test substance.

GROUP C

4.73

Title Final report on the safety assessment of Glycol Stearate, Glycol Stearate SE, and Glycol Distearate

Date of report **1982.**

GLP **No.**

Test substance CAS: 627-83-8, Glycol distearate, purity not indicated.

Guideline Not indicated.

Stat. method Not applicable.

Test system

Species	rabbit	rabbit	rabbit	rabbit
No. animals	3/sex/dose group	3/sex/dose group	3/sex/dose group	5/sex/dose group
Dosage	5/week 91 days to intact or abraded skin of 0.05-0.5%	5/week 28 days to intact or abraded skin of 0.05-0.5%	5/week 28 days to intact or abraded skin of 0.05-0.4%	5/week 28 days to intact or abraded skin of 0.05-0.3% (containing 1-3% test substance)
Observations	Not indicated	Gross and microscopic examination	Gross and microscopic examination	Not indicated
Results	No effects	No effects (skin irritation slight to severe)	No effects	No effects (slight transient skin irritation)

Conclusions No systemic toxic effects.

Klimisch criterium 4 Limited report, secondary literature.

4.74

Title 28 Day consecutive dose oral subacute test in rats

Date of report September 25, 1981.

GLP No.

Test substance CAS: 70729-68-9, purity: 88%, 6% triethylene glycol di-n-heptanoate, 4% mixed ester of tetraethylene glycol with n-heptanoic and 2 methylhexanoic acids, 2% other mixed esters.

Guideline Not indicated.

Stat. method ANOVA.

Test system

Species Rat (Wistar).

No. of animals 5/sex/treatment.

Dosage Oral administration (gavage) for 28 days at 0 and 1000 mg/kg bw, vehicle corn oil (1 l-1 5% solution); 14 day recovery period for 5 additional animals/sex receiving 1000 mg/kg bw.

Observations Clinical signs/body weight daily.
Blood sampling pretest, on day 28 and 42 (recovery).
Macroscopy/organ weights/limited histopathology on day 28 (main group and control) and 42 (recovery).

Results

Dose mg/kg bw)	0		1000		1000 (rec.)		DR	
Sex	M	F	M	F	M	F	M	F
Mortality	0/5	0/5	0/5	0/5	0/5	0/5		
Clinical signs (A)			+					
Body weight gain			d	d	d	d		
Haematology	No treatment related effects							
Leukocytes (day 0, 28, 42)								
Clinical biochemistry								
ASAT (day 28)								
ALP (day 40)				d	d	d		
Bilirubin (day 28)								
Organ weight	Not reported							
Necropsy	No treatment related effects							
Histopathology(B)	No treatment related effects							

(A) Congestion was seen.

(B) In all treatment groups and control lung lesions were seen (pneumonitis, peribronchiolitis and/or perivasculitis). Other findings were incidental and included cysts in Kürsteiners duct of the thyroid, thyroid C-cell hyperplasia, periportal vacuolisation, hepatitis, trachitis, nephritis, atrophy and degeneration of the seminiferous tubules of the testes and epididymitis.

Conclusions NOAEL 1000 mg/kg bw

Rev. note

1. No analytical determination of the test concentrations. No analyses for stability and homogeneity of the test substance.
2. Organ weights were not reported. All histopathological changes were linked to macroscopic effects.
3. Leukocyte counts were decreased compared to pretest values in both treated and control animals. In treated males pretest, 28-day and 42–day values were increased compared to the values in control males. Therefore these effects were considered to be of no toxicological relevance
4. The decreased levels of alkaline phosphatase were considered to be of no toxicological relevance.
5. The increased bilirubin level was found both in treated and control animals.
6. Since body weight loss was reported to be sporadic and effects on liver enzymes were not very clearly treatment related, 1000 mgkg bw is considered to be a NOAEL.
7. *Minor remarks.* Food intake was not measured. No information was available on age and weight of the animals, on housing conditions. Histopathology was limited (female sex organs, spinal cord, heart, urinary bladder and peripheral nerve tissue were not investigated)
8. Only the results for clinical chemistry, haematology and histopathology were reported. Other findings were summarised (no actual values and no individual data). Some of the blood parameters were stated to differ significantly from control values, however, this was not indicated in the tables in the report.

Klimisch criterium 2 Limited report (note 7 and 8), no analyses (note 1).

4.75

Title Subacute inhalation toxicity study of CAS: 70729-68-g in rats

Date of report November 4, 1981.

GLP No.

Test substance CAS: 70729-68-9, purity: 88%, 6% triethylene glycol di-n-heptanoate, 4% mixed ester of tetraethylene glycol with n-heptanoic and 2 methylhexanoic acids, 2% other mixed esters.

Guideline Not indicated.

Stat. method ANOVA, least significant difference, Dunnett's test.

Test system

Species Rat (Wistar), weight 240-266 g.

No. of animals 10 males/treatment.

Dosage Whole body exposure to 0 and 1 .0 mg/L, 6 hours/day, 5 days/week for 4 weeks; 14 day recovery period for 5 males/treatment group.

Procedure Heating of the test material between 230 and 250 °C. The vapour was carried on N_2 into 20L exposure chambers; O_2 218%; temperature < 30°C.

Analyses At 30 min intervals samples were trapped in acetone and analysed by GC/FID (standards in acetone were included).

Observations Clinical signs/body weight on weekdays. Macroscopy/organ weights/limited histopathology on 5 animals/treatment after 20 exposure days and on the other 5 animals/treatment after 14 days recovery.

Results

Analyses Overall recovery of test substance 1.1 ± 0.35 mg/L (mean ± SD). No results from analytical standards presented.

Dose (measured in mg/L)	0	1.1	1.1	DR
Mortality	None			
Clinical signs (A)		+	+	
Body weight gain	No treatment related effects			
Organ weight	No treatment related effects			
Necropsy	No treatment related effects			
Histopathology (B)	No treatment related effects			

(A) Salivation, reduced response to sound and shallow rapid respiration were noted during exposure. During the recovery period one rat had slight lung noise and one showed a brown-stained nose.

(B) In all treatment groups and control lung lesions were seen (severe focal pneumonitis, haemorrhage and/or oedema). Other findings were incidental and included centrilobular eosinophilic inclusions and lymphoid cell foci in the liver, nephritis and a microgranuloma in a hair follicle.

Conclusions LOAEL 1 .1 mg/L.

Rev. note

1. All histopathological changes were linked to macroscopic effects.
2. No blood parameters were included.
3. The temperature in the exposure chambers was high (up to 30°C). This may lead to an increased breathing rate and a concomitant increased uptake of the test substance. Since this may represent a worst case scenario, the validity of the study is not affected.
4. *Minor remarks.* Food intake was not measured. Histopathology was limited (spinal cord, urinary bladder and peripheral nerve tissue were not investigated).
5. The air flow in the exposure chambers is not indicated. According to OECD 412 12-l 5 air changes per hour are considered necessary.
6. Only the results for body weight, organ weights and histopathology were reported. Other findings were summarised (no actual values and no individual data).
7. The clinical signs observed in the treated animals could not be attributed to the lung lesions, since control animals showed similar severe lung lesions, but did not show the clinical effects. Therefore the 1 .1 mg/L is considered to be a LOAEL.

Klimisch criterium 2 Limited report (note 2, 4 and 6).

GROUP D

4.76

Title Final report on the safety assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate

Date of report 1985.

GLP No.

Test substance CAS: 1338-41-6, Sorbitan stearate, purity not indicated.

Guideline Not indicated.

Stat. method Not applicable.

Species	Rat (Wistar)
No. animals	12 males and 20 females treatment
Dosage	2-year dietary administration of 0, 5, 10 and 20%
Critical effects	Mortality of infants, increased liver, increased kidney weight
NOAEL	5% in diet

Conclusion NOAEL <2250 mgikg bw.

Rev. note The dietary intake was calculated by the reviewer, assuming a mean body weight of 500 g and mean food intake of 45 g/kg.

Klimisch criterium 4 Limited report, secondary literature.

4.77

Title Final report on the safety assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate

Date of report 1985.

GLP No.

Test substance CAS: 1338-39-2, Sorbitan laurate, purity not indicated.

Guideline Not indicated.

Stat. method Not applicable.

Test system

Species	rat	rat	rat	rat
No. animals	12 (sex not indicated)	15/sex/treatment	5/sex/treatment	1 O/sex/treatment
Dosage	6-weeks dietary administration of 0, 1 and 4%	90-day dietary administration of 0, 2.5, 5 and 10%	2 or 6 weeks dietary administration of 0, 5 and 10%	23 weeks dietary administration of 0, 15, 20 and 25%
Critical effects	Decreased growth	Decreased body weight, Hb, haematocrite, weight of heart and GI-tract Increased brain liver and kidney weight Periportal vacuolisation of hepatocytes, and tubular necrosis	Decreased body weight, Hb, haematocrite, weight of heart and GI-tract Increased brain liver and kidney weight Periportal vacuolisation of hepatocytes, and tubular necrosis	Diarrhoea, unkempt appearance, retarded growth Pale and enlarged liver, enlarged common bile duct and gangrene of tail Focal nephritis, hyperplasia of bone marrow and spleen and increased number of macrophages in lung
NOAEL	< 1% in diet			<10% in diet

Species	hamster	rat (Sprague Dawley)	rat	rat
No. animals	36 (sex not indicated)	14 (sex not indicated)	14 males. 16 females	10 males
Dosage	6-weeks dietary administration of 0, 5 and 15%	59-day dietary administration of 25%	59-day dietary administration of 25%	17 weeks dietary administration of 0 and 10%
Critical effects	Decreased growth and mortality GI mucosal hyperaemia and oedema, renal tubular degeneration	Weight loss, diarrhoea and nasal haemorrhage	Decreased body weight, activity and appetite Nasal bleeding and gangrene of the tail and hind legs Increased weight of brain, kidneys, heart, spleen, lungs and liver Degenerative changes of GI-tract, kidneys and liver	Decreased body weight, haematocrit and Hb Increased liver and kidney weight
NOAEL	< 5 % in diet	<25% in diet	<25% in diet	<10% in diet

Conclusion NOAEL <1% in diet < ~ 580 mg/kg bw
Rev. note The dietary intake was calculated by the reviewer, assuming a mean body weight of 300 g and a mean food intake of 17.5 g/rat/day.
Klimisch criterium 4 Limited report, secondary literature.

4.78
Title Final report on the safety assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate
Date of report 1985.
GLP No.
Test substance CAS: 1338-43-8, Sorbitan oleate, purity not indicated.
Guideline Not indicated.
Stat. method Not applicable.
Test system

Species	rat	rat	rat
No. animals	15/sex	5/sex	30-50 males
Dosage	16-weeks dietary administration of 0, 2.5, 5 and 10%	2 or 6-weeks dietary administration of 0, 5 and 10%	2-year dietary administration of 0 and 5%
Critical effects	Reduced body weight gain Increased liver and kidney weight Reduced haematocrit Fatty change of hepatocytes, renal tubular degeneration	Reduced body weight gain Increased liver and kidney weight Reduced haematocrit Fatty change of hepatocytes, renal tubular degeneration	None
NOAEL	<2.5% in diet	< 5% in diet	5% in diet

Conclusion NOAEL < 2.5% in diet ⇔ <~1450 mg/kg bw
Rev. note The dietary intake was calculated by the reviewer, assuming a mean body weight of 300 g and a mean food intake of 17.5 g/rat/day.
Klimisch criterium 4 Limited report, secondary literature.

4.79

Title	Final report on the safety assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate
Date of report	1985.
GLP	No.
Test substance	CAS: 8007-43-0, Sorbitan sesquioleate, purity not indicated.
Guideline	Not indicated.
Stat. method	Not applicable.
Test system	

Species	Rabbit (New Zealand White)
No. animals	9 females/treatment
Dosage	Dermal application of 0, 30, 300 and 3000 mg/kg (4% formulation in hormone cream) for 13 weeks (5 days/week).
Critical effects	Irritation Dose related increase of uterine and splenic weight, dose related decrease of liver weight
NOAEL	-

Conclusion	-
Rev. note	The effects were attributed to the hormone by the author of the report. An additional group without hormonal cream was included in the test design, but the results from this group were not reported. Therefore the statement of the author could not be checked.
Klimisch criterium	4 Limited report, secondary literature.

4.80

Title	Final report on the safety assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate
Date of report	1985.
GLP	No.
Test substance	CAS: 26266-58-0, Sorbitan trioleate, purity not indicated.
Guideline	Not indicated.
Stat. method	Not applicable.
Test system	

Species	Rabbit
No. animals	5/sex/treatment
Dosage	Dermal application of 0.12 ml/kg bw (5% formulation) for 93 days.
Critical effects	Slight erythema with incidental oedema, desquamation.
NOAEL	<0.006 ml/kg bw.

Conclusion	NOAEL < 0.006 ml/kg bw.
Rev. note	The density of the substance is not known, therefore it is not possible to calculate the administered dose.
Klimisch criterium	4 Limited report, secondary literature.

4.81

Title Final report on the safety assessment of Sorbitan Stearate, Sorbitan Laurate, Sorbitan Sesquioleate, Sorbitan Oleate, Sorbitan Tristearate, Sorbitan Palmitate, and Sorbitan Trioleate

Date of report 1985.

GLP No.

Test substance CAS: 1338-41-6, Sorbitan stearate, purity not indicated.

Guideline Not indicated.

Stat. method Not applicable.

Test system

Species	Rabbit (New Zealand White)	Rat (Osborne-Mendel)	Dog	Mouse (TO)
No. animals	5/sex/treatment, 7/sex/control	12/sex/treatment	4	48/sex/treatment
Dosage	3-months dermal application of 0 (water), 380 and 640 mg/kg bw	2-year dietary administration of 0, 2,510 and 25%	20-months dietary administration of 0 and 5%	80-weeks dietary administration of 0, 0.5, 2.0 and 4.0%
Critical effects	Erythema, oedema and desquamation	Mortality	None	Reduced body weight and decreased weight of brain, kidney, stomach and spleen in males
NOAEL	< 380 mg/kg bw (local)	5% in diet	5% in diet	<0.5% in diet

Conclusion NOAEL < 380 mg/kg bw

Rev. note The dietary intake was calculated by the reviewer, assuming a mean body weights and mean food intakes. The dermal dose was calculated based on a surface area of 1700 cm^2 and a body weight of 2.5 kg for rabbits.

Klimisch criterium 4 Limited report, secondary literature.

4.82

Title Short-term toxicity study of sorbitan monolaurate **(CAS:** 1338-39-2) in rats

Date of report **1978.**

GLP **No.**

Test substance CAS: 1338-39-2, purity not indicated.

Guideline Not indicated.

Stat. method Student's t-test, ranking method of White.

Test system

Species Rat (Wistar), weight 84-86 g (males), 69-71 g (females).

No. of animals 15/sex/dose level.

Dosage Dietary administration for 90 days at 0, 2.5, 5 and 10 mg/kg diet (no vehicle).

Observations Mainly as required by OECD 408 (no ophthalmoscopy, no behavioural effects, limited blood biochemistry, no blood clotting potential and limited histopathology (no parathyroid, oesophagus, trachea, mammary gland, prostate, bone marrow, skin and eyes)).

Results

Dose (% in diet)	0		2.5		5		10		DR	
Dose (g/kg bw)	0	0	2.1	2.3	4.2	4.5	8.0	8.4		
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Mortalitv	None									
Clinicalsigns	No treatment related effects									
Body weight			dc	d	dc	dc	dc	dc	x	x
Food consumption			dc	d	dc	dc	dc	dc	x	x
Water consumption					ic			dc		
Haematology										
Hb/haematocrit					dc	dc	dc	dc	x	x
RBC[A]			dc		dc			ic		
Leukocytes			dc		dc		dc		x	
Clinical biochemistry	Not reported									
Urinalysis [B]	No treatment *elated effects									
Organ weight										
Brain			ic^r	ic'	ic^r	ic^r	ic^r	ic^r	x	x
Kidney			ic^r	ic^r	ic^r	ic^r	ic^r	ic^r		x
Liver							ic^r	ic^r		
GI-tract					ic^r	ic^r	ic'	ic^r	x	x
Heart							ic^r	ic^r		
Histopathology [C]										
Liver - periportal vacuolation							+	+		
- increased periportal fat						+	+	+		

(A) There was a tendency for higher reticulocytes counts.
(B) Among treated males less urinary production with higher specific gravity.
(C) Signs of early respiratory disease were reported among animals.

Conclusion NOAEL < 2100 mg/kg bw
Rev. note The test substance is not sufficiently identified.
Klimisch criterium 2 Limited report and no identity of the test substance.

4.83

Title Chronic oral toxicities of four stearic acid emulsifiers
Date of report 1959.
GLP No.
Test substance CAS: 1338-41-6, purity not indicated.
Guideline Not indicated.
Stat. method Not indicated.
Test system
Species Rat (Osborne-Mendel), weight 40-50 g.
No. of animals 12/sex/dose level.
Dosage Dietary administration for 2 years at 0, 2, 5, 10 and 25% .
Observations Body weight/food consumption weekly.
Clinical signs/mortality frequently
Haematology (Hb, RBC, WBC and differential counts) on 10 animals twice during the study.
Organ weight of all survivors.
Necropsy/histopathology on all animals.

Results

Dose (% in diet)	0		2		5		10		25		DR	
Dose (g/kg bw)	0	0	1.3	1.5	3.3	3.8	8.7	7.5	25	24		
Sex	M	F	M	F	M	F	M	F	M	F	M	F
Mortality	12/24		12/24		14/24		18/24		18/24		x	x
Clinical signs	Not reported											
Body weight gain (wk 12)									dc	dc		
Food consumption										d		
Haematology	No treatment related effects											
Organ weight												
Liver									ic[r]			
Kidney									ic[r]			
Necropsy	Not reported											
Histopathology (A)									+			

(A) Fatty changes of the liver (hepatic cell vacuolisation) was reported among animals.

Conclusions NOAEL 3.8 g/kg bw.

Rev. note
1. The report was limited to the above mentioned.
2. The actual test substance intake was calculated by the reviewer, based on the reported food intake in control and high dosed animals and a mean body weight of 200 g for females and 300 g for males over the first 12 weeks. For the high dose group (with decreased body weight) 150 and 200 g were taken for females and males, resp..
3. The test substance is not sufficiently identified.

Klimisch criterium 3 Limited report, no identity of the test substance.

4.84

Title Chronic oral toxicities of four stearic acid emulsifiers

Date of report 1959.

GLP No.

Test substance CAS: 1338-41-6, purity not indicated.

Guideline Not indicated.

Stat. method Not indicated.

Test system

Species Dog (Mongrel or Irish terrier), l-6 years.

No. of animals 2/sex/dose level.

Dosage Dietary administration for 21 months at 5%; diets were adjusted for nutritional contribution by the test substance.

Observations Body weight / food consumption.
Necropsy / histopathology.

Results

Dose (% in diet)	0		5		DR	
Dose (mg/kg bw)	0	0	640-650	485-783		
Sex	M	F	M	F	M	F
Mortality	None					
Clinical signs	No treatment related effects					
Body weight/food consumption	No treatment related effects					
Necropsy	No treatment related effects					
Histopathology (A)			+	+		

(A) Hemosiderosis in Kupfer cells and macrophages.

Conclusions LOAEL 485 mg/kg bw.

Rev. note
1. The report was limited to the above mentioned.
2. The test substance is not sufficiently identified.

Klimisch criterium 4 Limited report, no identity of the test substance, secondary literature.

4.85

Title	Short-term toxicity study of sorbitan mono-oleate **(CAS:** 1338-43-8) in rats
Date of report	1978.
GLP	**No.**
Test substance	CAS: 1338-43-8, purity not indicated.
Guideline	Not indicated.
Stat. method	Not indicated.
Test system	**Species** Rat (Wistar), weight 89-94 g (males), 90-91 g (females).
	No. of animals 15sex/dose level; 1 O/sex/dose level (except at 2.5%) for interim kills after 2 or 6 weeks.
	Dosage Dietary administration for 16 weeks at 0, 2.5, 5 and 10%.
	Observations Mainly as per OECD 408 with limited haematology and clinical biochemistry, no ophthalmoscopy and no behavioural observations

Results

Dose (% in diet)	**0**		**2.5**		**5**		**10**		**DR**	
Dose (g/kg bw)	**0**	**0**	**1.7**	**2.0**	**3.1**	**3.7**	**6.3**	**5.1**		
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Mortality	None									
Clinical signs	No treatment related effects									
Body weight (day 105)							dc	dc		
Food consumption					d		dc	dc	x	
Water consumption					dc		dc	d	x	
Haematology										
HB/RBC								dc		
Haematocrit					dc		dc	dc	**x**	**x**
Leukocytes							dc			
Biochemistry										
Protein / albumin • wk 2					dc					
• wk6					dc		dc			
Urea					dc(wk6)			dc(wkl6)ll		
Urinalysis (A)	No treatment related effects									
Organ weights										
Brain							ic^r	i^r		
Heart					i'	ic^r	ic^r	ic^r		
Liver / small intestine							ic^r	ic^r		
Kidney			ic^r	ic^r	ic^r	ic^r	ic^r	ic^r	**x**	**x**
Stomach / adrenals							ic^r	ic^r		
pituitary / gonads										
Necropsy (wk 16)	Not reported									
Histopathology (wk 16)(B)						+		+		

(A) Effects seen included increased gravity and decreased volume.
(B) Renal tubular damage (dilation of proximal tubulus with vacuolisation) and periportal fatty changes of the liver.

Conclusion NOAEL < 1.7 g/kg bw.

Rev. note

1. The test substance is not sufficiently identified.
2. The dose levels tested may interfere with nutritional balance of the diet. This may be especially true for the two highest dose levels. Therefore it can not be excluded that part of the observations may have been caused by this nutritional imbalance.
3. The diet was not analysed for adequacy and homogeneity of preparation and no information on stability of the test substance (in the matrix) was provided.
4. The report is limited to the above mentioned.

Klimisch criterium 3 Limited report and no identity of the test substance.

GROUP E

4.66

Title	28-day dermal toxicity study in rats	
Date of report	February 13, 1997.	
GLP	Yes.	
Test substance	CAS: 11138-60-6, purity not indicated.	
Guideline	Not indicated.	
Stat. method	ANOVA, Dunnett's test.	
Test system	**Species**	Rat (Sprague Dawley), age 7 weeks, weight 147-220 g (males), 140-l 77 g (females).
	No. of animals	1 O/sex/dose level; additionally 1 O/sex in control and high dose group for 14-day recovery.
	Dosage	Dermal administration for 4 weeks (5 days/week) at 0, 125, 500 and 2000 mg/kg bw (no vehicle) on the clipped dorsal skin; untreated controls.
	Observations	Mainly as required by OECD 410.

Results

Dose mg/kg bw)	0		125		500		2000		2000 (rec)		DR	
Sex	M	F	M	F	M	F	M	F	M	F	M	F
Mortality					None							
Clinical signs (A)	+	+	+	+	+	+	+	+	+	+		
Local effects (B)			+	+	+	+	+	+	+	+		
Body weight			dc				dc	dc	dc	dc		
Body weight gain							dc	dc				
Food consumption (day O-7)							dc					
Haematology												
Lymphocytes				dc			dc					
Neutrophils				ic			ic	ic				
MHCH								dc				
RBC									dc	dc		
MCV									dc			
Hb										dc		
Clinical biochemistry												
Glucose							dc					
Creatinine					dc		dc	dc				
Albumin							dc	dc				
Albumin/globulin							dc		dc			
ALAT								ic		ic		
BUN				ic				ic				
Total bilirubin								dc				
Organ weight												
Kidney				ic[r]		ic'		ic[r]				
Liver								ic[r]				
Heart								ic[r]				
Brain							ic[r]	ic[r]				
Testes							ic[r]					
Thymus								dc[a]				
Necropsy	No trea lent relate effects											
Histopathology (C)	No treatment related effects											

(A) Symptoms included poor grooming, (red) staining around eyes and nose, scab formation (neck), sparse hair coat and hair loss. These effects can be attributed to the wearing of collars to prevent oral ingestion of the test substance.
(B) Effects included erythema, skin sloughing and paleness of the skin (no local effects during the first week of the study).
(C) Hypotrichosis, epidermal hyperplasia, epidermatitis, hyperkeratosis, oedema, ulceration, abscesses and foreign body granuloma were seen in the skin and subcutis of the neck region (related to the collars animals wore).

Conclusions NOAEL (systemic) 500 mg/kg bw.

Rev. note
1. The effects on organ weights can be related most probably to the lower body weights observed in high dosed animals. For relative kidney weight the effect was related to a slight, not significant reduction of body weight at 125 and 500 mg/kg in females.
2. The effects on the number of lymphocytes were coincidental, since they were not seen in the opposite sex. A decreased creatinine level is toxicological irrelevant.
3. In male recovery animals (2000 mg/kg bw) additionally increased levels of sodium, potassium, phosphate and triglicerides were seen.
4. The test substance is not sufficiently identified.
5. The application area was not indicated and may have been larger than 10% of the total body surface area. Since animals wore collars to prevent oral ingestion of the test substance, the test site was left uncovered (OECD 410 indicated a porous dressing to be applied), which may influence absorption.

Klimisch criterium 2 No identity of the test substance.

Reproduction toxicity

GROUP A

No data available.

GROUP B

4.88

Title Effects of **CAS: 16958-92-2** on fetal heart development following dermal application to pregnant rats

Date of report January 30, 1990.

GLP No.

Test substance CAS: 16958-92-2; di-tridecyl adipate, purity not indicated.

Guideline Not indicated.

Stat. method ANOVA , Fisher's Exact test, Dunnett's test; visceral data by ANOVA followed by Bartlett's test.

Test system

Species Rat (Sprague Dawley), 11 weeks old, mean weight 231-235 g..

No. of animals 25 mated females/treatment.

Dosage Dermal administration of at 0 and 2000 mg/kg bw (no vehicle) on the clipped dorsal skin; untreated and negative (XXXX, 2000 mg/kg) controls.

Procedures Female rats were mated with untreated males (1/1) from the same strain. The day of observation of a vaginal plug and spermatozoa in the vaginal lavage fluid was defined as day 0 of gestation. Females were treated daily from day 0 to 19 of gestation inclusive. Mortality/clinical symptoms of dams were noted daily from day 0 to 20. Body weight was recorded on day 0, 6, 10, 16 and 20. All females were subjected to macroscopic examination on day 20. The uteri were removed, weighed and examined for no. of corpora lutea, no. of implantation sites and no. and location of foetuses and resorptions. Foetuses were inspected on total number, sex, weight and external and visceral defects (½ of foetuses by the modified Wilson technique and ½ of the foetuses by Staples technique). Visceral examination was performed blind.

Results

Dose (mg/kg bw)	**0**	**CAS: 16958-92-2**	**xxxx**
Maternal data			
Mortality	0/25	0/25	0/25
Clinical signs (A)	+	+	+
Body weight gain		dc	dc
Uterus weight		No treatment related effects	
Necropsy		No treatment related effects	

No. of pregnant females	25	24	25
No. of corpora lutea and implantation sites /dam		No treatment related effects	
Pre-implantation loss			
Post-implantation loss/ resorptions		No treatment related effects	
No. live foetuses/ dam		No treatment related effects	
Foetal data			
No. of litters included in evaluations	15	13	13
Foetal weight		No treatment related effects	
External examination / sex		No treatment related effects	
Anomalies: visceral (Wilson)		No treatment related effects	
Visceral (Staples)		No treatment related effects	

(A) Among all animals: red nasal exudate, chromodacryorrhea and neck lesions (attributed to the wearing of Elizabethan collars) and dorsal scabs and scratches probably occurring during mating activity.
Among treated animals: erythema, oedema, flaking and scabs (effects more severe in XXXX treated animals).

Conclusions	No developmental toxicity observed.
Rev. note	1. The test was performed to examine whether the effects on foetal heart development found in a previous study (ref 72) could be reproduced. Furthermore influences of the visceral examination procedure on the results were compared. 2. The test substance is not sufficiently identified. 3. The application area was not indicated and may have been larger than 10% of the total body surface area. The test site was left uncovered (animals wore collars to prevent oral ingestion of the test substance), which may influence absorption. 4. *Minor remarks.* No staining of the non-gravid uteri was performed. Individual data were not included in the report presented to the reviewer.
Klimisch criterium	2 Inappropriate application (note 3) and no identity of the test substance (note 2).

4.89

Title	Developmental toxicity screen in rats exposed dermally to **CAS: 16958-92-2**	
Date of report	September 19, 1988.	
GLP	No.	
Test substance	CAS: 16958-92-2; di-tridecyl adipate, purity not indicated.	
Guideline	Not indicated.	
Stat. method	ANOVA, Fisher's Exact test, Dunnett's test (F-test and Student-Newman-Keul's multiple comparison test for blood biochemistry).	
Test system	**Species**	Rat (Sprague Dawley), 11 weeks old, mean weight 235-240 g.
	No. of animals	15 mated females/treatment.
	Dosage	Dermal administration of at 0, 800 and 2000 mg/kg bw (no vehicle) on the clipped dorsal skin; untreated controls.
	Procedures	Female rats were mated with untreated males (l/l) from the same strain. The day of observation of a vaginal plug and spermatozoa in the vaginal lavage fluid was defined as day 0 of gestation. Females were treated daily from day 0 to 19 of gestation inclusive. Mortality/clinical symptoms of dams were noted daily from day 0 to 20. Body weight / food consumption was recorded on day 0 (body weight only), 3, 6, 10, 13, 16 and 20. All females were subjected to macroscopic examination on day 20. The uteri were removed, weighed and examined for no. of corpora lutea, no. of implantation sites and no. and location of foetuses and resorptions. Foetuses were inspected on total number, sex, weight, length and external, visceral (½ of foetuses by the modified Wilson technique) and skeletal (½ of foetuses, cartilage and bone) defects. Blood was withdrawn on day 20 for clinical chemistry.

Results

Dose (mg/kg bw)	0	800	2000	DR
Maternal data				
Mortality	0/15	0/15	0/15	
Clinical signs (A)	+	+	+	
Body weight/body weight gain			dc	
Food intake - day 0-3		dc	dc	
- day 10-20		ic (d 16-20)	ic	
Uterus weight		No treatment related effects		
Necropsy		No treatment related effects		
Clinical chemistry				
ALAT/ALP		I	ic	x
Glucose		d	dc	x
Creatinine		dc	dc	x
Triglycerides/cholesterol		d	dc	x
Total protein/globulin		dc	dc	x
Fe		i	ic	x
No. of pregnant females	15	13	13	
No. of corpora lutea/ implantation sites /dam		No treatment related effects		
Pre- / post-implantation loss/ resorptions		No treatment related effects		
No. live foetuses/ dam		No treatment related effects		
Foetal data				
No. of litters included in evaluations	15	13	13	
Foetal weight / length		No treatment related effects		
External examination / sex		No treatment related effects		
Anomalies: visceral (B)			+	
skeletal (C)		No treatment related effects		

(A) Among all animals: red nasal exudate, chromodacryorrhea and neck lesions (attributed to the wearing of Elizabeth collars) and dorsal scabs and scratches probably occurring during mating activity.
Among treated animals: erythema, flaking and scabs.

(B) Malformations observed consisted of levocardia and hydronephrosis; renal variations were present (hydroplastic kidney, hydroureter, enlarged ureter and enlarged bladder).

(C) Incomplete ossification was seen among foetuses without apparent relation to treatment.

Conclusions NOAEL for maternal toxicity: <800 mg/kg.
NOAEL for reproductive effects: 800 mg/kg.

Rev. note
1. The test substance is not sufficiently identified.
2. The application area was not indicated and may have been larger than 10% of the total body surface area. The test site was left uncovered (animals wore collars to prevent oral ingestion of the test substance), which may influence absorption.
3. Alanine transferase, glucose, creatinine, cholesterol and iron were considered to be within ranges for historical controls by the author of the report.
4. Only 2 dose levels were tested and only 15 mated animals were included per dose group.
5. *Minor remarks.* No staining of the non-gravid uteri was performed. Individual data were not included in the report presented to the reviewer.

Klimisch criterium 2 Limited number of animals (note 4), inappropriate application (note 2) and no identity of the test substance (note 1).

GROUP C

No data available

GROUP D

4.90

Title	Nutritional studies on rats on diets containing high levels of partial ester emulsifiers	
Date of report	1956.	
GLP	**No.**	
Test substance	CAS: 1338-41-6, purity not indicated.	
Guideline	Not indicated.	
Stat. method	Not indicated.	
Test system	**Species**	Rat, age 110 days.
	No. of animals	12 males and 20 females per dose level in FO; 1 O/sex/dose level in other generations.
	Dosage	Dietary administration for 2 years (FO) at 0, 5, 10 and 20%.
	Design	The FO-generation received test diets for 12 weeks before mating (1 male/2 females) started. Animals of this generation were allowed to mate over the whole test period. Of the second litters of the FO, the F1 was selected. These animals were allowed two mating periods. This procedure was repeated until the F3 was born.
	Observations	Body weights every two weeks. Pup weight on day 4, 12 and 21 after birth. No. of matings, litters born alive, pups born alive.
Results	No effect on the time of loss of fertility was seen in the FO	

Dose (% in diet)	**0**	**5**	**10**	20	**DR**
Mortality/clinical signs			Not reported		
Body weight			Not reported		
F0					
Mean number of pups/litter - birth					
- weaning			d	d	x
Mean pup weight			d	d	x
F1					
Mean number of pups/litter - birth				d	
- weaning				d	
Mean pup weight			d	d	
F2					
Mean number of pups/litter - birth					
- weaning				d	
Mean pup weight				d	

Conclusions NOAEL 5% in diet.

Rev. note
1. The report was limited to the above mentioned.
2. Additionally a study was performed with an increased fat level in the diet. The number of surviving pups increased slightly by this adaption. However, it still cannot be excluded that part of the effects seen were related to nutritional imbalance, due to the high dose levels in the test.
3. The test substance is not sufficiently identified.

Klimisch criterium 3 Limited report, no identity of the test substance.

GROUP E

No data available

Other

GROUP A

No data available

GROUP B

No data available

GROUP C

No data available

GROUP D

4.92

Title	Studies on promoting action in skin carcinogenesis	
Date of report	**1963.**	
GLP	**No.**	
Test substance	CAS: 1338-41-6: CAS: 1338-39-2, purity not indicated.	
Guideline	Not indicated.	
Stat. method	Not indicated.	
Test system	**Species**	Mouse (Swiss).
	No. of animals	50/males/treatment.
	Dosage	Dermal administration for 66-75 weeks (2 times/week) of undiluted test substance on the clipped interscapular skin (2x2 cm) with and without initial single application of dimethylbenz(a)anthracene (DMBA, l-l .5% in mineral oil); untreated controls with initial application of DMBA.
	Observations	Twice weekly for skin lesions. No. of skin-tumour bearing animals, no. of tumours Histopathology of all animals suspected of bearing tumours.

Results

Dose mg/kg bw)	**0 (DMBA)**	**Treated**	**Treated (DMBA)**
Total duration of test (weeks)	66	73	75
Sex	**M**	**M**	**M**
Mortality (20 weeks)	13/50	28/50	24/50
No of tumour bearing animals	1	1	5
No of tumours	5	1	8
No of carcinomas	0	0	1

Conclusions	Non carcinogenic, minimal promoting activity
Rev. note	6. The report was limited to the above mentioned. 7. The application area was only -5% of the total body surface area. 8. The test substance was not sufficiently identified.
Klimisch criterium	3 Limited report (note 1) and no identity of the test substance (note 3).

4.93

Title A new and physicochemically well-defined group of tumur-promoting (cocarcinogenic) agents for mouse skin

Date of report November 23, 1954.

GLP No.

Test substance CAS: 1338-39-2, purity not indicated.

Guideline Not indicated.

Stat. method Not indicated.

Test system

Species Mouse, age 2 months.

No. of animals 50/treatment.

Dosage Dermal administration for 24 weeks (2 times/day) of undiluted test substance at the back with and without initial single application of dimethylbenz(a)anthracene (DMBA, 0.3% in paraffin oil): untreated controls with initial single application of DMBA.

Observations Mortality.
No. of skin-tumour bearing animals, no. of tumours

Results Results after 24 weeks are given.

Dose mg/kg bw)	0 (DMBA)	Treated	Treated (DMBA)
Sex	M	M	M
Mortality	0/50	n.i.	n.i.
No of tumour bearing animals	0	0	21
No of tumours	0	0	34

n.i. = not indicated.

Conclusions Promoting activity.

Rev. note
1. The report was limited to the above mentioned.
2. The test substance was not sufficiently identified.

Klimisch criterium 3 Limited report (note 1) and no identity of the test substance (note 2).

GROUP E

No data available

I U C L I D

D a t a S e t

Existing Chemical	Substance ID: 111-60-4
CAS No.	111-60-4
CAS Name	Octadecanoic acid, 2-hydroxy-, ethyl ester
Producer Related Part	
Company:	ENVIRON Corporation
Creation date:	17-NOV-2000
Substance Related Part	
Company:	ENVIRON Corporation
Creation date:	17-NOV-2000
Printing date:	30-JAN-2001
Revision date:	
Date of last Update:	30-JAN-2001
Number of Pages:	9
Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC

1.2 Synonyms

2-Hydroxyethyl stearate
19-NOV-2000

2.1 Melting Point

Value: 57 - 60 degree C
Method: other: no data
GLP: no data
Reliability: (2) valid with restrictions
22-NOV-2000 (6)

Value: = 60.5 degree C
Method: other: measured
GLP: no data
Reliability: (2) valid with restrictions
21-DEC-2000 (8)

2.2 Boiling Point

Value: 404.1 degree C
Method: other: estimated: adapted Stein and Brown Method
GLP: no
Result: at 1 atm pressure.
Reliability: (2) valid with restrictions
27-DEC-2000 (9)

2.3 Density

2.3.1 Granulometrs

2.4 Vapour Pressure

Method: other (calculated) : estimated (Modified Grain Method)
GLP: no
Result: 1.14E-08 mm Hg at 25 deg. C.
Reliability: (2) valid with restrictions
27-DEC-2000 (9)

Method: other (calculated): estimated
GLP: no data
Result: 6.6E-8 mm Hg at 25 deg. C.
Reliability: (2) valid with restrictions
27-DEC-2000 (5)

2.5 Partition Coefficient

log Pow: ca. 7.26 at 25 degree C
Method: other (calculated): estimated
GLP: no data
Reliability: (2) valid with restrictions
27-DEC-2000 (4)

2.6.1 Water Solubility

Value: ca. .0063 mg/l at 25 degree c
Method: other: estimated
GLP: no data
Reliability: (2) valid with restrictions
04-JAN-2001 (1)

Value: .017 mg/l at 25 degree C
Method: other: estimated
GLP: no
Reliability: (2) valid with restrictions
27-DEC-2000 (10)

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

2.9 Flammability

2.10 Explosive Properties

2.11 Oxidizing Properties

2.12 Additional Remarks

3.1.1 Photodegradation

3.1.2 Stability in Water

Type: abiotic
t1/2 pH7: ca. 7.7 year at 25 degree C
Method: other: estimated
Year: **GLP:** no
Test substance: as prescribed by 1.1 - 1.4
Result: The results of computer modeling indicate that 2-hydroxyethyl stearate is hydrolytically stable under ambient water conditions of 25 degrees C with a pH of 7. Hydrolysis results in release of the alcohol group and the free aliphatic acid. The estimated half-life of 2-hydroxyethyl stearate was 7.7 years.
Reliability: (2) valid with restrictions
30-JAN-2001 (2)

3.1.3 Stability in Soil

3.2 Monitoring Data (Environment)

3.3.1 Transport between Environmental Compartments

Type: other: EQC model
Media: water - soil
Method: other: estimated
Year:
Result: The environmental transport and distribution characteristics of 2-hydroxyethyl stearate were estimated using the EQC model (version 1.07; Level III), as recommended by the U.S. EPA. The data input for this model include molecular weight, melting point, water solubility, vapor pressure and octanol/water partition coefficient. The model was run assuming water to be the only source of emissions. The results indicate that sediment was the primary compartment for 2-hydroxyethyl stearate, which is entirely consistent with its physical/chemical properties, such as long alkyl chain length and relatively low water solubility. The distribution percentages of 2-hydroxyethyl stearate were 15.1% in water and 84.9% in sediment.
Reliability: (2) valid with restrictions
30-JAN-2001 (3)

3.3.2 Distribution

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type :
Inoculum: other: no data
Result: readily biodegradable
Method: other: estimated
Year: GLP: no
Test substance: as prescribed by 1.1 - 1.4
Remark: Biodegrades fast.
Reliability: (2) valid with restrictions
30-JAN-2001 (9)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

4.2 Acute Toxicity to Aquatic Invertebrates

4.3 Toxicitv to Aquatic Plants e.g. Algae

4.4 Toxicitv to Microorganisms e.g. Bacteria

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicitv to Fish

4.5.2 Chronic Toxicitv to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicitv to Soil Dwelling Organisms

4.6.2 Toxicitv to Terrestrial Plants

4.6.3 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type:	LD50
Species:	rat
Sex:	male/female
Number of Animals:	5
Vehicle:	other: corn oil
Value:	> 5000 mg/kg bw
Method:	other: no data
Year:	GLP: no data
Test substance:	as prescribed by 1.1 - 1.4
Result:	Five (5) male and 5 female Wistar rats weighing 200-300 grams were fasted for 18 hours and dosed by gavage with 5.0 g/kg body weight of test material. The test material was mixed with corn oil and administered as a 25% w/w solution. The rats were observed for mortality or other signs of gross toxicity for 14 days. Observations were unremarkable and necropsy was unremarkable. The oral LD50 of the test material was > 5000 mg/kg.
Reliability:	(2) valid with restrictions

14-DEC-2000 (7)

5.1.2 Acute Inhalation Toxicity

5.1.3 Acute Dermal Toxicity

5.1.4 Acute Toxicity, other Routes

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

5.2.2 Eye Irritation

5.3 Sensitization

5.4 Repeated Dose Toxicity

5.5 Genetic Toxicity 'in Vitro'

5.6 Genetic Toxicity 'in Vivo'

5.7 Carcinogenicity

5.8 Toxicity to Reproduction

5.9 Developmental Toxicity/Teratogenicity

5.10 Other Relevant Information

5.11 Experience with Human Exposure

(1) ECOSAR. Version 0.99d. Syracuse Research Corporation.

(2) HYDROWIN, version 1.67. Syracuse Research Corporation.

(3) Mackay et al. 1996. Environ. Toxicol. Chem. 15(9):1618-1626; 1627-1637; 1638-1648.

(4) Meylan & Howard. 1995. CITED IN: SRC PhysProp Database. Http://esc.syrres.com/. 3/2000.

(5) MPBPWIN. Version 1.40. Syracuse Research Corporation.

(6) SAX'S Dangerous Properties of Industrial Materials, 9th Ed.

(7) Spear. 1984. Acute Oral Toxicity. Report T-3912. Product Safety Labs.

(8) SRC PhysProp Database. Http://esc.syrres.com/. 3/2000.

(9) Weeg-Aerssens. 2000. EPIWIN. Tailored Environmental Programs, Inc.

(10) WSKowWIN. Version 1.40. Syracuse Research Corporation.

I U C L I D

D a t a S e t

Existing Chemical	Substance ID: 68002-79-g
CAS No.	68002-79-g
Generic name	C14-18 and C16-18 unsaturated fatty acid glycerides
Producer Related Part	
Company:	ENVIRON Corporation
Creation date:	17-NOV-2000
Substance Related Part	
Company:	ENVIRON Corporation
Creation date:	17-NOV-2000
Printing date:	15-DEC-2000
Revision date:	
Date of last Update:	**15-DEC-2000**
Number of Pages:	6
Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC

2.1 Melting Point

2.2 Boiling Point

2.3 Density

2.3.1 Granulometry

2.4 Vapour Pressure

2.5 Partition Coefficient

2.6.1 Water Solubility

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

2.9 Flammability

2.10 Explosive Properties

2.11 Oxidizing Properties

2.12 Additional Remarks

3.1.1 Photodegradation

3.1.2 Stability in Water

3.1.3 Stability in Soil

3.2 Monitoring Data (Environment)

3.3.1 Transport between Environmental Compartments

3.3.2 Distribution

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

Type:	aerobic
Inoculum:	other: municipal sewage effluent
Concentration:	100 mg/l related to COD (Chemical Oxygen Demand)
Contact time:	28 day
Result:	readily biodegradable
Method:	other: OECD ring test on ready biodegradability, two phase closed bottle test (based on OECD Guideline 301D).
Year:	GLP: no data
Test substance:	as prescribed by 1.1 - 1.4
Remark:	The test was conducted at a temperature of 20 deg. C in the dark for 28 days. The percentage BOD/COD or BOD/ThOD for the test material at a concentration of 100 mg COD/l was 86% after 28 days. Edenor GTO was biodegraded more than 60% BOD/COD or BOD/ThOD within a 14-day time window (according to OECD guidelines) and thus it was considered readily biodegradable.
Reliability:	(3) invalid

15-DEC-2000 (2)

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Brachydanio rerio (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l Analytical monitoring: no data
LC0: 3000
LC50: 5500
Method: OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year: GLP: no data
Test substance: as prescribed by 1.1 - 1.4
Result: In the static test, groups of zebra fish (Brachydanio rerio) were exposed to a range of concentrations of the test substance (at least 3000 and 10,000 mg/l) in water for a period of 96 hours. Mortality was recorded at least at 24-hour intervals and ultimately, the LCO and LC100 were determined. Based on these data, the LC50 was calculated. The highest tested concentration that had no mortality was 3000 mg active matter/l and the lowest tested concentration in which all the animals died was 10000 mg active matter/l. Thus the LC50 was 5500 mg active matter/l.
Reliability: (3) invalid
15-DEC-2000 (1)

4.2 Acute Toxicity to Aquatic Invertebrates

4.3 Toxicity to Aquatic Plants e.g. Algae

4.4 Toxicity to Microorganisms e.g. Bacteria

4.5 Chronic Toxicity to Aquatic Organisms

4.51 Chronic Toxicity to Fish

4.5.2 Chronic Toxicity to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

4.6.2 Toxicity to Terrestrial Plants

4.6.3 Toxicity to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.1 Acute Toxicitv

51.1 Acute Oral Toxicitv

51.2 Acute Inhalation Toxicitv

5.1.3 Acute Dermal Toxicitv

5.1.4 Acute Toxicitv, other Routes

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

5.2.2 Eve Irritation

5.3 Sensitization

5.4 Repeated Dose Toxicity

5.5 Genetic Toxicitv 'in Vitro'

5.6 Genetic Toxicitv 'in Vivo'

5.7 Carcinogenicity

5.8 Toxicity to Reproduction

5.9 Developmental Toxicity/Teratogenicity

5.10 Other Relevant Information

5.11 Experience with Human Exposure

(1) Steber & Berger. 2000. Acute Toxicity: Fish. Henkel KGaA. l-page summary.

(2) Steber & Berger. 2000. Aerobic Biodegradation: BODIS Test/Two-Phase Closed Bottle Test. Henkel KGaA. Report No. R9600281 (March 1996). l-page summary.

I U C L I D

D a t a S e t

Existing Chemical	Substance ID: 68130-53-o
CAS No.	68130-53-o
CAS Name	Decanoic acid, mixed esters with heptanoic and octanoic acids, and trimethylolpropane

Producer Related Part	
Company:	ENVIRON Corporation
Creation date:	17-NOV-2000
Substance Related Part	
Company:	ENVIRON Corporation
Creation date:	17-NOV-2000

Printing date:	27-DEC-2000
Revision date:	
Date of last Update:	27-DEC-2000

Number of Pages:	6

Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC

2.1 Melting Point

Value: ca. 148 degree C
Method: other: estimated
GLP: no
Reliability: (2) valid with restrictions
27-DEC-2000 (3)

2.2 Boiling Point

Value: ca. 505 degree C
Method: other: estimated
GLP: no
Result: at 1 atm. pressure.
Reliability: (2) valid with restrictions
27-DEC-2000 (3)

2.3 Density

2.3.1 Granulometrg

2.4 Vapour Pressure

Method: other (calculated) : estimated
GLP: no
Result: 1.1E-9 mm Hg at 25 deg. C.
Reliability: (2) valid with restrictions
27-DEC-2000 (3)

2.5 Partition Coefficient

log Pow: ca. 10.68 at 25 degree C
Method: other (calculated) : estimated
GLP: no
Reliability: (2) valid with restrictions
27-DEC-2000 (2)

2.6.1 Water Solubility

Method: other: estimated
GLP: no
Result: 3.19e-6 mg/l at 25 deg. C.

Reliability: (2) valid with restrictions
27-DEC-2000 (1)

Method: other: estimated
GLP: no
Result: 4.53-7 mg/l at 25 deg. C.
Reliability: (2) valid with restrictions
27-DEC-2000 (4)

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

2.9 Flammability

2.10 Explosive Properties

2.11 Oxidizing Properties

2.12 Additional Remarks

3.1.1 Photodegradation

3.1.2 Stability in Water

3.1.3 Stability in Soil

3.2 Monitoring Data (Environment)

3.3.1 Transport between Environmental Compartments

3.3.2 Distribution

3.4 Mode of Degradation in Actual Use

3.5 Biodegradation

3.6 BOD5, COD or BOD5/COD Ratio

3.7 Bioaccumulation

3.8 Additional Remarks

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicitv to Fish

4.2 Acute Toxicity to Aquatic Invertebrates

4.3 Toxicitv to Aquatic Plants e.g. Algae

4.4 Toxicity to Microorganisms e.g. Bacteria

4.5 Chronic Toxicitv to Aquatic Organisms

4.5.1 Chronic Toxicitv to Fish

4.5.2 Chronic Toxicitv to Aquatic Invertebrates

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

4.6.2 Toxicitv to Terrestrial Plants

4.6.3 Toxicitv to other Non-Mamm. Terrestrial Species

4.7 Biological Effects Monitoring

4.8 Biotransformation and Kinetics

4.9 Additional Remarks

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

5.1.2 Acute Inhalation Toxicity

5.1.3 Acute Dermal Toxicity

5.1.4 Acute Toxicity, other Routes

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

5.2.2 Eye Irritation

5.3 Sensitization

5.4 Repeated Dose Toxicity

5.5 Genetic Toxicity 'in Vitro'

5.6 Genetic Toxicity 'in Vivo'

5.7 Carcinogenicity

5.8 Toxicity to Reproduction

5.9 Developmental Toxicity/Teratogenicity

5.10 Other Relevant Information

5.11 Experience with Human Exposure

(1) ECOSAR. Version 0.99d. Syracuse Research Corporation.

(2) KowWIN. Version 1.66. Syracuse Research Corporation.

(3) MPBPWIN. Version 1.40. Syracuse Research Corporation.

(4) WsKowWIN. Version 1.40. Syracuse Research Corporation.